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Transmitted herewith for filing under 37 CFR §1.53(c) is the PROVISIONAL APPLICATION for patent of

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TITLE OF THE INVENTION (280 characters max)

ORGANIC COMPOUNDS

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- ☒ Specification (Including Any Claims and Abstract) - 69 pages
- ☐ Drawings - sheets
- ☒ Other (specify): Application Data Sheet

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Respectfully submitted,

Lyd McNally

Date: April 7, 2004

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ORGANIC COMPOUNDS

The present invention relates generally to novel compounds that inhibit the binding of the Smac protein to Inhibitor of Apoptosis Proteins (IAPs). The present invention includes novel compounds, novel compositions, methods of their use and methods of their manufacture, where such compounds are generally pharmacologically useful as agents in therapies whose mechanism of action rely on the inhibition of the Smac/IAP interaction, and more particularly useful in therapies for the treatment of proliferative diseases, including cancer.

BACKGROUND

Programmed cell death plays a critical role in regulating cell number and in eliminating stressed or damaged cells from normal tissues. Indeed, the network of apoptotic signaling mechanisms inherent in most cell types provides a major barrier to the development and progression of human cancer. Since most commonly used radiation and chemo-therapies rely on activation of apoptotic pathways to kill cancer cells, tumor cells which are capable of evading programmed cell death often become resistant to treatment.

Apoptosis signaling networks are classified as either intrinsic when mediated by death receptor-ligand interactions or extrinsic when mediated by cellular stress and mitochondrial permeabilization. Both pathways ultimately converge on individual Caspases. Once activated, Caspases cleave a number of cell death-related substrates, effecting destruction of the cell.

Tumor cells have devised a number of strategies to circumvent apoptosis. One recently reported molecular mechanism involves the overexpression of members of the IAP family. IAPs sabotage apoptosis by directly interacting with and neutralizing Caspases. The prototype IAPs, XIAP and cIAP have three functional domains referred to as BIR 1, 2 & 3 domains. BIR3 domain interacts directly with

Caspase 9 and inhibits its ability to bind and cleave its natural substrate, Procaspase 3.

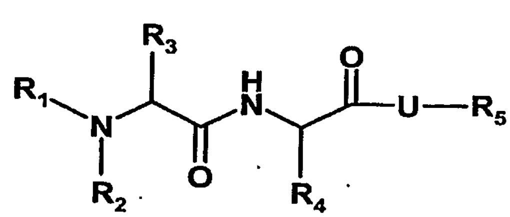
It has been reported that a proapoptotic mitochondrial protein, Smac (also known as DIABLO), is capable of neutralizing XIAP and/or cIAP by binding to a peptide binding pocket (Smac binding site) on the surface of BIR3 thereby precluding interaction between XIAP and/or cIAP and Caspase 9. The present invention relates to therapeutic molecules that bind to the Smac binding pocket thereby promoting apoptosis in rapidly dividing cells. Such therapeutic molecules are useful for the treatment of proliferative diseases, including cancer.

Summary of the Invention

The present invention relates generally to novel compounds that inhibit the binding of the Smac protein to Inhibitor of Apoptosis Proteins (IAPs). The present invention includes novel compounds, novel compositions, methods of their use and methods of their manufacture, where such compounds are generally pharmacologically useful as agents in therapies whose mechanism of action rely on the inhibition of the Smac/IAP interaction, and more particularly useful in therapies for the treatment of proliferative diseases, including cancer.

DETAILED DESCRIPTION

The present invention relates to compounds of the formula (I)



(I)

wherein

R_1 is H; C_1-C_4 alkyl, C_1-C_4 alkenyl, C_1-C_4 alkynyl or cycloalkyl which are unsubstituted or substituted;

R_2 is H, C_1-C_4 alkyl, C_1-C_4 alkenyl, C_1-C_4 alkynyl or cycloalkyl which are unsubstituted or substituted;

R_3 is H, $-CF_3$, $-C_2F_5$, C_1-C_4 alkyl, C_1-C_4 alkenyl, C_1-C_4 alkynyl; $-CH_2$-Z or R_2 and R_3 together with the nitrogen form a het ring;

Z is H, –OH, F, Cl, $-CH_3$; $-CF_3$, $-CH_2Cl$, $-CH_2F$ or $-CH_2OH$;

R_4 is C_1-C_{16} straight or branched alkyl, C_1-C_{16} alkenyl, C_1-C_{16} alkynyl, or cycloalkyl, -$(CH_2)_{1-6}$-Z_1, -$(CH_2)_{0-6}$-phenyl, and -$(CH_2)_{0-6}$-het, wherein alkyl, cycloalkyl and phenyl are unsubstituted or substituted;

Z_1 is –N(R_8)-C(O)-C_1-C_{10}alkyl, –N(R_8)-C(O)-$(CH_2)_{1-6}$-C_3-C_7-cycloalkyl, –N(R_8)-C(O)-$(CH_2)_{0-6}$-phenyl, –N(R_8)-C(O)-$(CH_2)_{1-6}$-het, -C(O)-N(R_9)(R_{10}), -C(O)-O-C_1-C_{10}alkyl, -C(O)-O-$(CH_2)_{1-6}$-C_3-C_7-cycloalkyl, -C(O)-O-$(CH_2)_{0-6}$-phenyl, -C(O)-O-$(CH_2)_{1-6}$-het, -O-C(O)-C_1-C_{10}alkyl, -O-C(O)-$(CH_2)_{1-6}$-C_3-C_7-cycloalkyl, -O-C(O)-$(CH_2)_{0-6}$-phenyl, -O-C(O)-$(CH_2)_{1-6}$-het, wherein alkyl, cycloalkyl and phenyl are unsubstituted or substituted;

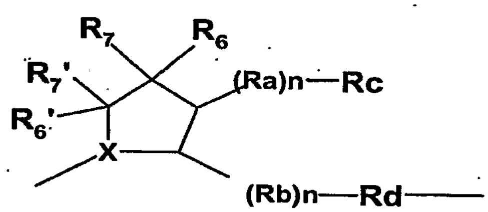
het is a 5-7 membered heterocyclic ring containing 1- 4 heteroatoms selected from N, O and S, or an 8-12 membered fused ring system including at least one 5-7 membered heterocyclic ring containing 1, 2 or 3 heteroatoms selected from N, O, and S, which heterocyclic ring or fused ring system is unsubstituted or substituted on a carbon or nitrogen atom;

R_8 is H, $-CH_3$, $-CF_3$, $-CH_2OH$ or CH_2Cl;

R_9 and R_{10} are each independently H, C_1-C_4alkyl, C_3-C_7-cycloalkyl, -$(CH_2)_{1-6}$-C_3-C_7-cycloalkyl, -$(CH_2)_{0-6}$-phenyl, wherein alkyl, cycloalkyl and phenyl are unsubstituted or substituted, or R_9 and R_{10} together with the nitrogen form het;

R_5 is H, C_1-C_{10}-alkyl, C_3-C_7-cycloalkyl, -$(CH_2)_{1\text{-}6}$-C_3-C_7-cycloalkyl, -C_1-C_{10}-alkyl-aryl, -$(CH_2)_{0\text{-}6}$-C_3-C_7-cycloalkyl-$(CH_2)_{0\text{-}6}$-phenyl, -$(CH_2)_{0\text{-}4}$CH-($(CH_2)_{1\text{-}4}$-phenyl)$_2$, -$(CH_2)_{0\text{-}6}$-CH(phenyl)$_2$, -indanyl, -C(O)-C_1-C_{10}alkyl, -C(O)-$(CH_2)_{1\text{-}6}$-C_3-C_7-cycloalkyl, -C(O)-$(CH_2)_{0\text{-}6}$-phenyl, -$(CH_2)_{0\text{-}6}$-het , -C(O)-$(CH_2)_{1\text{-}6}$-het, or R_5 is a residue of an amino acid, wherein the alkyl, cycloalkyl, phenyl and aryl substituents are unsubstituted or substituted;

U is a as shown in structure II:



II

wherein

n = 0-5;

X is –CH or N;

Ra and Rb are independently an O, S, or N atom or $C_{0\text{-}8}$ alkyl wherein one or more of the carbon atoms in the alkyl chain may be replaced by a heteroatom selected from O, S or N, and where the alkyl may be unsubstituted or substituted;

Rd is selected from:

(a) -Re – Q – (Rf)(Rg); or

(b) Ar_1–D– Ar_2 ;

Rc is H or Rc and Rd may together form a cycloalkyl or het; where if Rd and Rc form a cycloalkyl or het, R_5 is attached to the formed ring at a C or N atom;

Re is $C_{1\text{-}8}$ alkyl which may be unsubstituted or substituted;

Q is N, O, S, S(O), or S(O)$_2$;

Ar_1 and Ar_2 are substituted or unsubstituted aryl or het;

Rf and Rg are each independently H or substituted or unsubstituted C_0-C_{10}-alkyl or C_1-C_{10}-alkylaryl;

D is –CO-, or C_{1-7} alkyl, aryl which may be unsubstituted or substituted with one or more halogens, OH, -O-C_1-C_6alkyl, -S-C_1-C_6alkyl or -CF_3;

R_6, R_7, R'_6 and R'_7 are each independently H, -C_1-C_{10} alkyl, -OH, -O-C_1-C_{10}-alkyl, -$(CH_2)_{0-6}$-C_3-C_7-cycloalkyl, -O-$(CH_2)_{0-6}$-aryl, phenyl, -$(CH_2)_{1-6}$-het, -O-$(CH_2)_{1-6}$-het, -OR_{11}, -C(O)-R_{11}, –C(O)-N(R_{11})(R_{12}), -N(R_{11})(R_{12}), -S-R_{11}, -S(O)-R_{11}, -$S(O)_2$-R_{11}, -$S(O)_2$-$NR_{11}R_{12}$, -NR_{11}-$S(O)_2$- R_{12}, wherein alkyl, cycloalkyl and aryl are unsubstituted or substituted; and R_6, R_7, R'_6 and R'_7 can be united to form a ring system;

R_{11} and R_{12} are independently H, C_1-C_{10} alkyl, -$(CH_2)_{0-6}$-C_3-C_7-cycloalkyl, -$(CH_2)_{0-6}$-$(CH)_{0-1}$$(aryl)_{1-2}$, -C(O)-$C_1$-$C_{10}$alkyl, -C(O)-$(CH_2)_{1-6}$-$C_3$-$C_7$-cycloalkyl, -C(O)-O-$(CH_2)_{0-6}$-aryl, -C(O)-$(CH_2)_{0-6}$-O-fluorenyl, -C(O)-NH-$(CH_2)_{0-6}$-aryl, -C(O)-$(CH_2)_{0-6}$-aryl, -C(O)-$(CH_2)_{1-6}$-het, -C(S)-$C_1$-$C_{10}$alkyl, -C(S)-$(CH_2)_{1-6}$-$C_3$-$C_7$-cycloalkyl, -C(S)-O-$(CH_2)_{0-6}$-aryl, -C(S)-$(CH_2)_{0-6}$-O-fluorenyl, -C(S)-NH-$(CH_2)_{0-6}$-aryl, -C(S)-$(CH_2)_{0-6}$-aryl, -C(S)-$(CH_2)_{1-6}$-het, wherein alkyl, cycloalkyl and aryl are unsubstituted or substituted; or R_{11} and R_{12} are a substituent that facilitates transport of the molecule across a cell membrane; or R_{11} and R_{12} together with the nitrogen atom form het;
wherein the alkyl substituents of R_{11} and R_{12} may be unsubstituted or substituted by one or more substituents selected from C_1-C_{10}, halogen, OH, -O-C_1-C_6alkyl, -S-C_1-C_6alkyl or -CF_3;
substituted cycloalkyl substituents of R_{11} and R_{12} are substituted by one or more substituents selected from a C_1-C_{10} alkene, C_1-C_6alkyl, halogen, OH, -O-C_1-C_6alkyl, -S-C_1-C_6alkyl or -CF_3; and
substituted phenyl or aryl of R_{11} and R_{12} are substituted by one or more substituents selected from halogen, hydroxy, C_1-C_4 alkyl, C_1-C_4 alkoxy, nitro, -CN, -O-C(O)-C_1-C_4alkyl and –C(O)-O-C_1-C_4-aryl,
or pharmaceutically acceptable salts thereof.

The present invention also related to the use of compound of formula I in the treatment of proliferative diseases, especially those dependent on the binding of the Smac protein to Inhibitor of Apoptosis Proteins (IAPs), or for the manufacture of pharmaceutical compositions for use in the treatment of said diseases, methods of use of compounds of formula (I) in the treatment of said diseases, pharmaceutical preparations comprising compounds of formula (I) for the treatment of said diseases, compounds of formula (I) for use in the treatment of said diseases.

The general terms used hereinbefore and hereinafter preferably have within the context of this disclosure the following meanings, unless otherwise indicated:

"Aryl" is an aromatic radical having 6 to 14 carbon atoms, which may be fused or unfused, and which is unsubstituted or substituted by one or more, preferably one or two substituents, wherein the substituents are as described below. Preferred "aryl" is phenyl, naphthyl or indanyl.

"Het" refers to heteroaryl and heterocyclic rings and fused rings containing aromatic and non-aromatic heterocyclic rings. "Het" is a 5-7 membered heterocyclic ring containing 1- 4 heteroatoms selected from N, O and S, or an 8-12 membered fused ring system including at least one 5-7 membered heterocyclic ring containing 1, 2 or 3 heteroatoms selected from N, O, and S Suitable het substituents include unsubstituted and substituted pyrrolidyl, tetrahydrofuryl, tetrahydrothiofuranyl, piperidyl, piperazyl, tetrahydropyranyl, morphilino, 1,3-diazapane, 1,4-diazapane, 1,4-oxazepane, 1,4-oxathiapane, furyl, thienyl, pyrrole, pyrazole, triazole, thiazole, oxazole, pyridine, pyrimidine, isoxazolyl, pyrazine, quinoline, isoquinoline, pyridopyrazine, pyrrolopyridine, furopyridine, indole, benzofuran, benzothiofuran, benzindole, benzoxazole, pyrroloquinoline, and the like. The het substituents are unsubstituted or substituted on a carbon atom by halogen, especially fluorine or chlorine, hydroxy, C_1-C_4 alkyl, such as methyl and ethyl, C_1-C_4 alkoxy, especially methoxy and ethoxy, nitro, -O-C(O)-C_1-C_4alkyl or –C(O)-O-C_1-C_4-alkyl or on a

nitrogen by C_1-C_4 alkyl, especially methyl or ethyl, -O-C(O)-C_1-C_4alkyl or –C(O)-O-C_1-C_4-alkyl, such as carbomethoxy or carboethoxy.

When two substituents together with a commonly bound nitrogen are het, it is understood that the resulting heterocyclic ring is a nitrogen-containing ring, such as aziridine, azetidine, azole, piperidine, piperazine, morphiline, pyrrole, pyrazole, thiazole, oxazole, pyridine, pyrimidine, isoxazolyl, and the like.

Halogen is fluorine, chlorine, bromine or iodine, especially fluorine and chlorine.

Unless otherwise specified "alkyl" includes straight or branched chain alkyl, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, n-pentyl and branched pentyl, n-hexyl and branched hexyl, and the like.

A "cycloalkyl" group means C_3 to C_{10}-cycloalkyl having 3 to 8 ring carbon atoms and may be, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl. Preferably, cycloalkyl is cycloheptyl. The cycloalkyl group may be unsubstituted or substituted with any of the substituents defined below, preferably halo, hydroxy or C_1-C_4 alkyl such as methyl.

The amino acid residues include a residue of a standard amino acid, such as alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine. The amino acid residues also include the side chains of uncommon and modified amino acids. Uncommon and modified amino acids are known to those of skill in the art (see for example G. B. Fields, Z. Tiam and G Barany; Synthetic Peptides A Users Guide, University of Wisconsin Biochemistry Center, Chapter 3, (1992)) and include amino acids such as 4-hydroxyproline, 5-hydroxylysine, desmosine, beta-alanine, alpha, gamma- and beta-aminobutric acid, homocysteine, homoserine, citrulline, ornithine, 2- or 3-amino adipic acid, 6-aminocaproic acid, 2- or 3- aminoisobutric acid, 2,3-diaminopropionic

acid, diphenylalanine, hydroxyproline and the like. If the side chain of the amino acid residue contains a derivatizable group, such as COOH, -OH or amino, the side chain may be derivatized by a substituent that reacts with the derivatizable group. For example, acidic amino acids, like aspartic and glutamic acid, or hydroxy substituted side chains, like those of serine or threonine, may be derivatized to form an ester, or amino side chains may form amide or alkylamino derivatives. In particular, the derivative may be a substituent that facilitates transport across a cell membrane. In addition, any carboxylic acid group in the amino acid residue, for example, an alpha carboxylic acid group, may be derivatized as discussed above to form an ester or amide.

Substituents that facilitate transport of the molecule across a cell membrane are known to those of skill in the medicinal chemistry arts (see, for example, Gangewar S., Pauletti G. M.,Wang B., Siahaan T. J., Stella V. J., Borchardt R. T., *Drug Discovery Today*, vol. 2. p148-155 (1997) and Bundgaard H. and Moss J., *Pharmaceutical Research*, vol. 7, p 885 (1990)). Generally, such substituents are lipophillic substituents. Such lipophillic substituents include a C_6-C_{30} alkyl which is saturated, monounsaturated, polyunsaturated, including methylene-interrupted polyene, phenyl, phenyl which substituted by one or two C_1-C_8 alkyl groups, C_5-C_9 cycloalkyl, C_5-C_9 cycloalkyl which is substituted by one or two C_1-C_8 alkyl groups, -X_1-phenyl, -X_1-phenyl which is substituted in the phenyl ring by one or two C_1-C_8 alkyl groups, X_1-C_5-C_9 cycloalkyl or X_1-C_5-C_9 cycloalkyl which is substituted by one or two C_1-C_8 alkyl groups; where X_1 is C_1-C_{24} alkyl which is saturated, monounsaturated or polyunsaturated and straight or branched chain.

Unsubstituted is intended to mean that hydrogen is the only substituent.

Any of the above defined aryl, het, alkyl, cycloalkyl, or heterocyclic groups may be unsubstituted or independently substituted by up to four, preferably one, two or three substituents, selected from the group consisting of: halo (such as Cl or Br); hydroxy; lower alkyl (such as C_1-C_3 lower alkyl); lower alkyl which may be substituted with any

of the substituents defined herein; lower alkenyl; lower alkynyl; lower alkanoyl; alkoxy (such as methoxy); aryl (such as phenyl or benzyl); substituted aryl (such as fluoro phenyl or methoxy phenyl); amino; mono- or disubstituted amino; amino lower alkyl (such as dimethylamino); acetyl amino; amino lower alkoxy (such as ethoxyamine); nitro; cyano; cyano lower alkyl; carboxy; esterified carboxy (such as lower alkoxy carbonyl e.g. methoxy carbonyl); n-propoxy carbonyl or iso-propoxy carbonyl; alkanoyl; benzoyl; carbamoyl; N-mono- or N,N-disubstituted carbamoyl; carbamates; alkyl carbamic acid esters; amidino; guanidine; urea; ureido; mercapto; sulfo; lower alkylthio; sulfoamino; sulfonamide; benzosulfonamide; sulfonate; sulfanyl lower alkyl (such as methyl sulfanyl); sulfoamino; substituted or unsubstituted sulfonamide (such as benzo sulfonamide); substituted or unsubstituted sulfonate (such as chloro-phenyl sulfonate); lower alkylsulfinyl; phenylsulfinyl; phenyl-lower alkylsulfinyl; alkylphenylsulfinyl; lower alkanesulfonyl; phenylsulfonyl; phenyl-lower alkylsulfonyl; alkylphenylsulfonyl; halogen-lower alkylmercapto; halogen-lower alkylsulfonyl; such as especially trifluoromethane sulfonyl; phosphono ($-P(=O)(OH)_2$); hydroxy-lower alkoxy phosphoryl or di-lower alkoxyphosphoryl; substituted urea (such as 3-trifluoro-methyl-phenyl urea); alkyl carbamic acid ester or carbamates (such as ethyl-N-phenyl-carbamate) or $-NR_4R_5$, wherein R_4 and R_5 can be the same or different and are independently H; lower alkyl (e.g. methyl, ethyl or propyl); or R_4 and R_5 together with the N atom form a 3- to 8-membered heterocyclic ring containing 1-4 nitrogen, oxygen or sulfur atoms (e.g. piperazinyl, pyrazinyl, lower alkyl-piperazinyl, pyridyl, indolyl, thiophenyl, thiazolyl, n-methyl piperazinyl, benzothiophenyl, pyrrolidinyl, piperidino or imidazolinyl) where the heterocyclic ring may be substituted with any of the substituents defined herein.

Preferably the above mentioned alkyl, cycloalkyl, aryl or het groups may be substituted by halogen, carbonyl, thiol, S(O), $S(O_2)$, -OH, -SH, $-OCH_3$, $-SCH_3$, -CN, -SCN or nitro.

Where the plural form is used for compounds, salts, pharmaceutical preparations, diseases and the like, this is intended to mean also a single compound, salt, or the like.

It will be apparent to one of skill in the art when a compound of the invention can exist as a salt form, especially as an acid addition salt or a base addition salt. When a compound can exist in a salt form, such salt forms are included within the scope of the invention. Although any salt form may be useful in chemical manipulations, such as purification procedures, only pharmaceutically acceptable salts are useful for pharmaceutically products.

Pharmaceutically acceptable salts include, when appropriate, pharmaceutically acceptable base addition salts and acid addition salts, for example, metal salts, such as alkali and alkaline earth metal salts, ammonium salts, organic amine addition salts, and amino acid addition salts, and sulfonate salts. Acid addition salts include inorganic acid addition salts such as hydrochloride, sulfate and phosphate, and organic acid addition salts such as alkyl sulfonate, arylsulfonate, acetate, maleate, fumarate, tartrate, citrate and lactate. Examples of metal salts are alkali metal salts, such as lithium salt, sodium salt and potassium salt, alkaline earth metal salts such as magnesium salt and calcium salt, aluminum salt, and zinc salt. Examples of ammonium salts are ammonium salt and tetramethylammonium salt. Examples of organic amine addition salts are salts with morpholine and piperidine. Examples of amino acid addition salts are salts with glycine, phenylalanine, glutamic acid and lysine. Sulfonate salts include mesylate, tosylate and benzene sulfonic acid salts.

In view of the close relationship between the compounds in free form and those in the form of their salts, including those salts that can be used as intermediates, for example in the purification or identification of the compounds, tautomers or tautomeric mixtures and their salts, any reference to the compounds hereinbefore and hereinafter especially the compounds of the formula I, is to be understood as referring also to the corresponding tautomers of these compounds, especially of

compounds of the formula I, tautomeric mixtures of these compounds, especially of compounds of the formula I, or salts of any of these, as appropriate and expedient and if not mentioned otherwise.

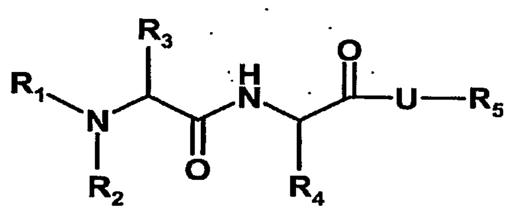
Any asymmetric carbon atom may be present in the (R)-, (S)- or (R,S)-configuration, preferably in the (R)- or (S)-configuration. Substituents at a ring at atoms with saturated bonds may, if possible, be present in cis- (= Z-) or trans (= E-) form. The compounds may thus be present as mixtures of isomers or preferably as pure isomers, preferably as enantiomer-pure diastereomers or pure enantiomers.

Preferred embodiments according to the invention:

In the following preferred embodiments, general expression can be replaced by the corresponding more specific definitions provided above and below, thus yielding stronger preferred embodiments of the invention.

Preferred is the USE of compounds of the formula I or pharmaceutically acceptable salts thereof, where the disease to be treated is a proliferative disease depending on binding of the Smac protein to inhibitor of Apoptosis Proteins (IAPS).

An embodiment of the present invention relates to compounds of the formula (I)



(I)

wherein

R_1 is H; C_1-C_4 alkyl, C_1-C_4 alkenyl, C_1-C_4 alkynyl or cycloalkyl which are unsubstituted or substituted by one or more substituents selected from halogen, -OH, -SH, $-OCH_3$, $-SCH_3$, -CN, -SCN and nitro;

R_2 is H, C_1-C_4alkyl, C_1-C_4 alkenyl, C_1-C_4 alkynyl or cycloalkyl which are unsubstituted or substituted by one or more substituents selected from halogen, -OH, -SH, $-OCH_3$, $-SCH_3$, -CN, -SCN and nitro;

R_3 is H, $-CF_3$, $-C_2F_5$, C_1-C_4 alkyl, C_1-C_4 alkenyl, C_1-C_4 alkynyl; $-CH_2$-Z or R_2 and R_3 together with the nitrogen form a het;

Z is H, –OH, F, Cl, $-CH_3$; $-CF_3$, $-CH_2Cl$, $-CH_2F$ or $-CH_2OH$;

R_4 is C_1-C_{16} straight or branched alkyl, C_1-C_{16} alkenyl, C_1-C_{16} alkynyl, or cycloalkyl, $-(CH_2)_{1-6}$-Z_1, $-(CH_2)_{0-6}$-phenyl, and $-(CH_2)_{0-6}$-het, wherein alkyl, cycloalkyl and phenyl are unsubstituted or substituted;

Z_1 is $-N(R_8)$-C(O)-C_1-C_{10}alkyl, $-N(R_8)$-C(O)-$(CH_2)_{1-6}$-C_3-C_7-cycloalkyl, $-N(R_8)$-C(O)-$(CH_2)_{0-6}$-phenyl, $-N(R_8)$-C(O)-$(CH_2)_{1-6}$-het, -C(O)-$N(R_9)(R_{10})$, -C(O)-O-C_1-C_{10}alkyl, -C(O)-O-$(CH_2)_{1-6}$-C_3-C_7-cycloalkyl, -C(O)-O-$(CH_2)_{0-6}$-phenyl, -C(O)-O-$(CH_2)_{1-6}$-het, -O-C(O)-C_1-C_{10}alkyl, -O-C(O)-$(CH_2)_{1-6}$-C_3-C_7-cycloalkyl, -O-C(O)-$(CH_2)_{0-6}$-phenyl, -O-C(O)-$(CH_2)_{1-6}$-het, wherein alkyl, cycloalkyl and phenyl are unsubstituted or substituted;

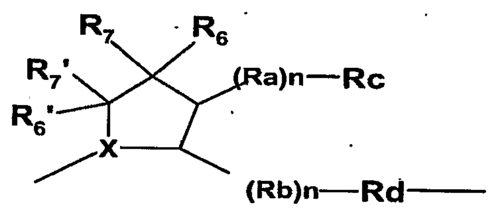
het is a 5-7 membered heterocyclic ring containing 1- 4 heteroatoms selected from N, O and S, or an 8-12 membered fused ring system including at least one 5-7 membered heterocyclic ring containing 1, 2 or 3 heteroatoms selected from N, O, and S, which heterocyclic ring or fused ring system is unsubstituted or substituted on a carbon atom by halogen, hydroxy, C_1-C_4alkyl, C_1-C_4 alkoxy, nitro, -O-C(O)-C_1-C_4alkyl or –C(O)-O-C_1-C_4-alkyl or on a nitrogen by C_1-C_4 alkyl, -O-C(O)-C_1-C_4alkyl or –C(O)-O-C_1-C_4-alkyl;

R_8 is H, $-CH_3$, $-CF_3$, $-CH_2OH$ or CH_2Cl;

R_9 and R_{10} are each independently H, C_1-C_4alkyl, C_3-C_7-cycloalkyl, $-(CH_2)_{1-6}$-C_3-C_7-cycloalkyl, $-(CH_2)_{0-6}$-phenyl, wherein alkyl, cycloalkyl and phenyl are unsubstituted or substituted, or R_9 and R_{10} together with the nitrogen form het;

R_5 is H, C_1-C_{10}-alkyl, C_3-C_7-cycloalkyl, -$(CH_2)_{1\text{-}6}$-C_3-C_7-cycloalkyl, -C_1-C_{10}-alkyl-aryl, -$(CH_2)_{0\text{-}6}$-C_3-C_7-cycloalkyl-$(CH_2)_{0\text{-}6}$-phenyl, -$(CH_2)_{0\text{-}4}$CH-($(CH_2)_{1\text{-}4}$-phenyl$)_2$, -$(CH_2)_{0\text{-}6}$-CH(phenyl$)_2$, -indanyl, -C(O)-C_1-C_{10}alkyl, -C(O)-$(CH_2)_{1\text{-}6}$-C_3-C_7-cycloalkyl, -C(O)-$(CH_2)_{0\text{-}6}$-phenyl, -$(CH_2)_{0\text{-}6}$-het , -C(O)-$(CH_2)_{1\text{-}6}$-het, or R_5 is a residue of an amino acid, wherein alkyl, cycloalkyl, phenyl and aryl are unsubstituted or substituted;

U is a as shown in structure II:



II

wherein

n = 0-5;

X is –CH or N;

Ra and Rb are independently an O, S, or N atom or $C_{0\text{-}8}$ alkyl wherein one or more of the carbon atoms in the alkyl chain may be replaced by a heteroatom selected from O, S or N, and where the alkyl may be unsubstituted or substituted;

Rd is selected from:

(c) Re – Q – (Rf)(Rg) ; or

(d) Ar_1–D– Ar_2 ;

Rc is H or Rd and Rc together form cycloalkyl or het; where if Rd and Rc form a cycloalkyl or heteroring, R_5 is attached to the formed ring at a C or N atom;

Re is $C_{1\text{-}8}$ alkyl which may be unsubstituted or substituted;

Q is N, O, S, S(O), or $S(O)_2$;

Ar_1 and Ar_2 are substituted or unsubstituted aryl or het;

Rf and Rg are each independently H or substituted or unsubstituted C_0-C_{10}-alkyl or C_1-C_{10}-alkylaryl;

D is –CO–, or C_{1-7} alkyl which may be unsubstituted or substituted with one or more halogens, OH, -O-, C_1-C_6alkyl, -S-C_1-C_6alkyl or -CF_3;

and R_6, R_7, R'_6 and R'_7 are each independently H, -C_1-C_{10} alkyl, -OH, -O-C_1-C_{10}-alkyl, -$(CH_2)_{0\text{-}6}$-C_3-C_7-cycloalkyl, -O-$(CH_2)_{0\text{-}6}$-aryl, phenyl, -$(CH_2)_{1\text{-}6}$-het, -O-$(CH_2)_{1\text{-}6}$-het, -OR_{11}, -C(O)-R_{11}, –C(O)-N(R_{11})(R_{12}), -N(R_{11})(R_{12}), -S-R_{11}, -S(O)-R_{11}, -$S(O)_2$-R_{11}, -$S(O)_2$-$NR_{11}R_{12}$, -NR_{11}-$S(O)_2$- R_{12}, wherein alkyl, cycloalkyl and aryl are unsubstituted or substituted; or any R_6, R_7, R'_6 and R'_7 can be united to form a ring system;
R_{11} and R_{12} are independently H, C_1-C_{10} alkyl, -$(CH_2)_{0\text{-}6}$-C_3-C_7-cycloalkyl, -$(CH_2)_{0\text{-}6}$-$(CH)_{0\text{-}1}$$(aryl)_{1\text{-}2}$, -C(O)-$C_1$-$C_{10}$alkyl, -C(O)-$(CH_2)_{1\text{-}6}$-$C_3$-$C_7$-cycloalkyl, -C(O)-O-$(CH_2)_{0\text{-}6}$-aryl, -C(O)-$(CH_2)_{0\text{-}6}$-O-fluorenyl, -C(O)-NH-$(CH_2)_{0\text{-}6}$-aryl, -C(O)-$(CH_2)_{0\text{-}6}$-aryl, -C(O)-$(CH_2)_{1\text{-}6}$-het, -C(S)-$C_1$-$C_{10}$alkyl, -C(S)-$(CH_2)_{1\text{-}6}$-$C_3$-$C_7$-cycloalkyl, -C(S)-O-$(CH_2)_{0\text{-}6}$-aryl, -C(S)-$(CH_2)_{0\text{-}6}$-O-fluorenyl, -C(S)-NH-$(CH_2)_{0\text{-}6}$-aryl, -C(S)-$(CH_2)_{0\text{-}6}$-aryl, -C(S)-$(CH_2)_{1\text{-}6}$-het, wherein alkyl, cycloalkyl and aryl are unsubstituted or substituted; or R_{11} and R_{12} are a substituent that facilitates transport of the molecule across a cell membrane; or R_{11} and R_{12} together with the nitrogen are het; aryl of R_{11} and R_{12} can be phenyl, naphthyl, or indanyl which is unsubstituted or substituted;
alkyl of R_{11} and R_{12} may be unsubstituted or substituted by one or more substituents selected from a C_1-C_{10} alkene, halogen, OH, -O-C_1-C_6alkyl, -S-C_1-C_6alkyl and -CF_3;
cycloalkyl of R_{11} and R_{12} may be unsubstituted or substituted by one or more selected from a C_1-C_{10} alkene, one or more halogens, C_1-C_6alkyl, halogen, OH, -O-C_1-C_6alkyl, -S-C_1-C_6alkyl or -CF_3; and
phenyl or aryl of R_{11} and R_{12} may be unsubstituted or substituted by one or more substituents selected from halogen, hydroxy, C_1-C_4 alkyl, C_1-C_4 alkoxy, nitro, -CN, -O-C(O)-C_1-C_4alkyl and –C(O)-O-C_1-C_4-aryl;
or pharmaceutically acceptable salts thereof.

A further embodiment the present invention relates to the use of compound of formula I in the treatment of proliferative diseases, especially those dependent on the binding of the Smac protein to Inhibitor of Apoptosis Proteins (IAPs), or for the manufacture of pharmaceutical compositions for use in the treatment of said diseases, methods of use of compounds of formula (I) in the treatment of said diseases, pharmaceutical preparations comprising compounds of formula (I) for the treatment of said diseases, compounds of formula (I) for use in the treatment of said diseases.

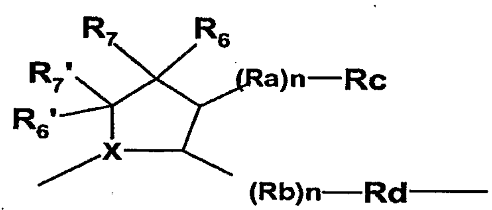
One embodiment of the present invention relates to compounds of the formula (I) wherein

R_1 and R_2 are independently H or substituted or unsubstituted C_1-C_4alkyl;

R_4 is C_1-C_{16} straight or branched alkyl, or cycloalkyl, wherein the alkyl or cycloalkyl may be unsubstituted or substituted;

R_5 is H, C_1-C_{10}-alkyl, C_1-C_{10}-alkyl-aryl, indanyl, naphthyl or R_5 is a residue of an amino acid, wherein the alkyl or aryl substituents are unsubstituted or substituted;

U is a as shown in structure II:



II

wherein

n = 0-5;

X is –CH or N;

Ra and Rb are independently an O, S, or N atom or $C_{0\text{-}8}$ alkyl wherein one or more of the carbon atoms in the alkyl chain may be replaced by a heteroatom selected from O, S or N, and where the alkyl may be unsubstituted or substituted;

Rd is selected from

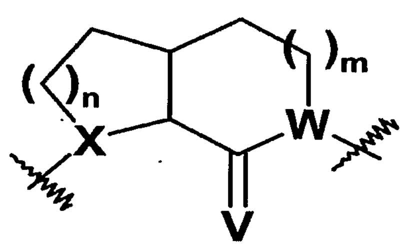
(e) --Re – Q – (Rf)(Rg); or

(f) Ar_1–D– Ar_2;

Rc is H or Rc and Rd together form cycloalkyl or het; where if Rd and Rc form a cycloalkyl or heteroring, R_5 is attached to the formed ring at a C or N atom;

Re is C_{1-8} alkyl which may be unsubstituted or substituted;
Q is N, O, S, S(O), or $S(O)_2$;
Ar_1 and Ar_2 are substituted or unsubstituted aryl or het;
Rf and Rg are each independently H or substituted or unsubstituted C_0-C_{10}-alkyl or C_1-C_{10}-alkylaryl;
D is –CO–, or C_{1-7} alkyl which may be unsubstituted or substituted with one or more halogens, OH, -O-C_1-C_6alkyl, -S-C_1-C_6alkyl or -CF_3;
and R_6, R_7, R'_6 and R'_7 are each independently H, -C_1-C_{10} alkyl, or –OH, alkoxy, or aryloxy;
or pharmaceutically acceptable salts thereof.

In a further embodiment, U is a bicyclic saturated or unsaturated ring system, consisting of all carbon skeleton or with one or more heteroatoms such as O, N, S but preferably as shown in structure III:



III

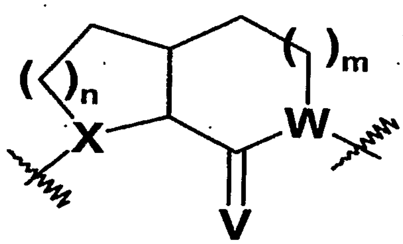
wherein
wherein any of the ring carbon atoms can be unsubstituted or substituted with any of the substituted defined above for R_6, R_7, $R_{6'}$ and R_7';
X is CH or N;
V is O, F_2, Cl_2, Br_2, I_2, S, YH, H_2, NH, or C_1-C_4 alkyl;
W is -CH, or -N;
n is 0-3; and

m is 0-3.

In a preferred embodiment the ring atoms may be substituted with subsituents independently selected from halo, H, OH, lower alkyl or lower alkoxy, wherein alkyl or alkoxy are unsubstituted or substituted by halogen, OH, lower alkyl or lower alkoxy.

In a further embodiment, U of formula II or III together with R_5 form a fused ring system.

Especially preferred is a compound of formula (I) wherein
R_1 and R_3 are preferably methyl or ethyl;
R_2 is especially H, methyl, ethyl, chloromethyl, dichloromethyl or trifluoromethyl;
R_4 is C_1-C_4alkyl or C_3-C_7 cycloalkyl particularly isopropyl, t-butyl, cyclopentyl, or cyclohexyl;
R_5 is -C_1-C_4-alkyl-phenyl, particularly phenylmethyl, phenylethyl and phenylpropyl; indanyl, naphthyl;
R_6 and R_7 are H or methyl;
U has the structure of formula III:



III

wherein

wherein any of the ring carbon atoms can be unsubstituted or substituted with any of the substituted defined above for R_6, R_7, $R_{6'}$ and R_7';
X is N;
V is O or H_2;

W is -N;
n is 1; and
m is 1 or 2.

Especially preferred is a compound of formula (I) wherein
R_1 and R_3 are preferably methyl or ethyl;
R_2 is H;
R_4 is C_1-C_4alkyl or C_3-C_7 cycloalkyl particularly isopropyl, t-butyl, or cyclohexyl;
R_5 is -C_1-C_4-alkyl-phenyl, particularly phenylethyl; indanyl, naphthyl;
R_6, R'_6, R_7 and R'_7 are H;
U has the structure of formula III wherein
wherein any of the ring carbon atoms can be unsubstituted or substituted with any of the substituted defined above for R_6, R_7, $R_{6'}$ and R_7';
X is N;
V is O or H_2;
W is -N;
n is 1; and
m is 1 or 2.

Another embodiment is directed to a compound of formula (I) wherein
R_1 and R_3 are preferably methyl or ethyl;
R_2 is especially H, methyl, ethyl, chloromethyl, dichloromethyl or trifluoromethyl;
R_4 is C_1-C_4alkyl or C_3-C_7 cycloalkyl particularly isopropyl, t-butyl, cyclopentyl, or cyclohexyl;
R_5 is H;
U has the structure of formula II wherein
X is N;
R_6, R'_6, R_7, and R'_7 are H;
n is O;
Rc is H;
Ar_1 and Ar_2 are phenyl and D is C_1 alkyl.

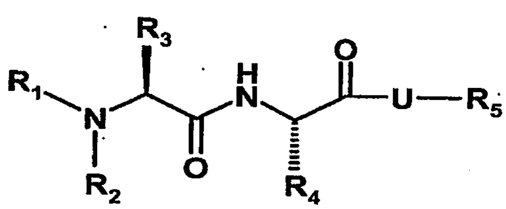
Another embodiment is directed to a compound of formula (I) wherein
R_1 and R_3 are preferably methyl or ethyl;
R_2 is especially H, methyl, ethyl, chloromethyl, dichloromethyl or trifluoromethyl;
R_4 is C_1-C_4alkyl or C_3-C_7 cycloalkyl particularly isopropyl, t-butyl, cyclopentyl, or cyclohexyl;
R_5 is H, indanyl or phenyl;
U has the structure of formula II wherein
X is N;
Q is O;
R_6, R'_6, R_7, and R'_7 are H;
n is O;
Re is C_1 alkyl; and
R_g and R_f are C_0 alkyl.

A further embodiment is directed to a compound of formula (I) wherein
R_1 and R_3 are preferably methyl or ethyl;
R_2 is especially H, methyl, ethyl, chloromethyl, dichloromethyl or trifluoromethyl;
R_4 is C_1-C_4alkyl or C_3-C_7 cycloalkyl particularly isopropyl, t-butyl, cyclopentyl, or cyclohexyl;
R_5 is H, indanyl or phenyl;
U has the structure of formula II wherein
X is N;
Q is N;
R_6, R'_6, R_7, and R'_7 are H;
n is O;
Re is C_1 alkyl; and
R_g is C_1 alkyl (methyl), C_2 alkyl(ethyl), or C_2 alkylphenyl;
and R_f is C_2 alkyl or C_2 alkylphenyl.

A further embodiment is directed to a compound of formula (I) wherein

R_1 and R_3 are preferably methyl or ethyl;
R_2 is especially H, methyl, ethyl, chloromethyl, dichloromethyl or trifluoromethyl;
R_4 is C_1-C_4alkyl or C_3-C_7 cycloalkyl particularly isopropyl, t-butyl, cyclopentyl, or cyclohexyl;
R_5 is phenyl;
U has the structure of formula II wherein
X is N;
Q is S, S(O) or $S(O)_2$;
R_6, R'_6, R_7, and R'_7 are H;
n is O;
Re is C_1 alkyl;
R_g is C_0 alkyl;
Rc is H;
and R_f is C_2 alkyl.

In a particularly important embodiment of the present invention, R_3 and R_4 have the stereochemistry indicated in formula IV, with the definitions of the variable substituents and preferences described herein above also applying to compounds having the stereochemistry indicated in formula IV.



IV

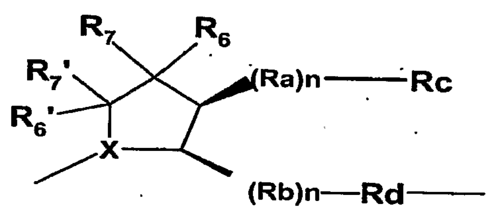
Especially preferred is a compound with the stereochemistry of formula (IV) wherein R_1 and R_3 are preferably methyl or ethyl;
R_2 is H, methyl, ethyl, or substituted methyl especially chloromethyl, dichloromethyl and trifluoromethyl; preferably R_2 is H or unsubstituted methyl;

R_4 is C_1-C_4alkyl or C_3-C_7 cycloalkyl particularly isopropyl, t-butyl, cyclopentyl, or cyclohexyl;

R_5 is -C_1-C_4-alkyl-phenyl, particularly phenylmethyl, phenylethyl and phenylpropyl, indanyl, naphthyl; and

R_6 and R_7 are H or methyl.

The preferred stereochemistry for U is as shown in Figure V



V

In a particular embodiment of the present invention, one or both of R_6, R_7, $R_{6'}$, and $R_{7'}$ is H. If one of R_6, R_7, $R_{6'}$, and $R_{7'}$ is other than H, it is especially hydroxyl or phenoxy.

Synthetic Procedure

Abbreviations:

CH_2Cl_2	methylene chloride
CH_3CN	acetonitrile
DIBAL	diisobutylaluminium hydride
DIPEA	diisopropylethylamine
DME	ethylene glycol dimethyl ether
DMF	*N, N*-dimethylformamide
DTBB	4,4'-di-tert-butylbiphenyl
EtOAc	ethyl acetate

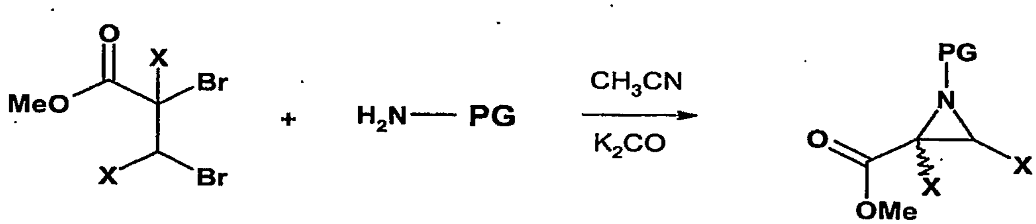
HBTU	*O*-benzyltriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
HOBt	1-hydroxhbenzotriazole
HPLC	high pressure liquid chromatography
KOTMS	potassium trimethysilanoate.
MeOH	methanol
$MgSO_4$	magnesium sulfate
MnO_2	manganese dioxide
Na_2CO_3	sodium carbonate
$NaHCO_3$	sodium bicarbonate
NaOH	sodium hydroxide
Tetrakis	tetrakis(triphenylphosphine)palladium(0)
TFA	trifluoroacetic acid
THF	tetrahydrofuran

The compounds of formula (I) may be prepared as depicted below in scheme 1 (for compound # 8 – 24, 28 - 30):

General synthesis scheme for compounds of formula 1 where W=N and X and X' are independently selected from the subsituents defined above for R_6:

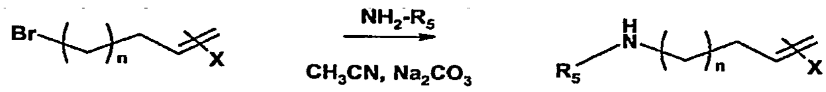
KOTMS is defined as potassium trimethysilanoate.

Step A



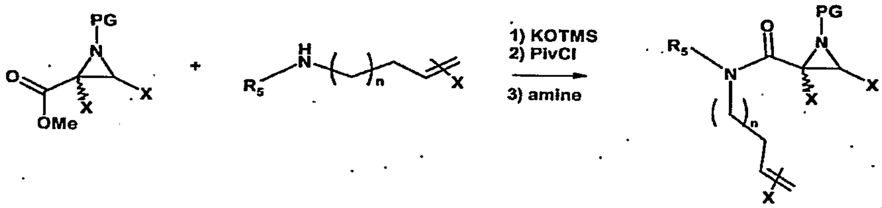
PG = benzyl or benzylic protecting group.

Step B



n = 0,1 or 2

Step C

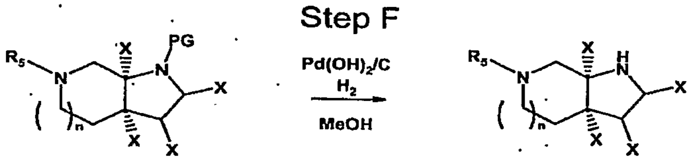


Step D

separate diastereomers

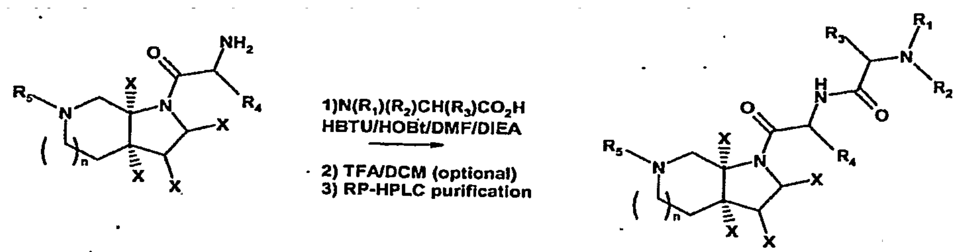
Step E

Step F



Step G

Step H



Scheme 1

Step A: This step involves the formation of an aziridine ring *via* standard base mediated conditions.

Step B: This step involves the formation of a secondary amine *via* the reaction of an alkyl bromide with excess amine in the presence of a base.

Step C: This step involves the coupling of a secondary amine with an activated derivative of the aziridine methyl ester to form an amide substituted aziridine.

Step D: This step involves the intramolecular cycloaddition of the aziridine to the tethered alkene through a thermally accessible azomethine ylide intermediate.

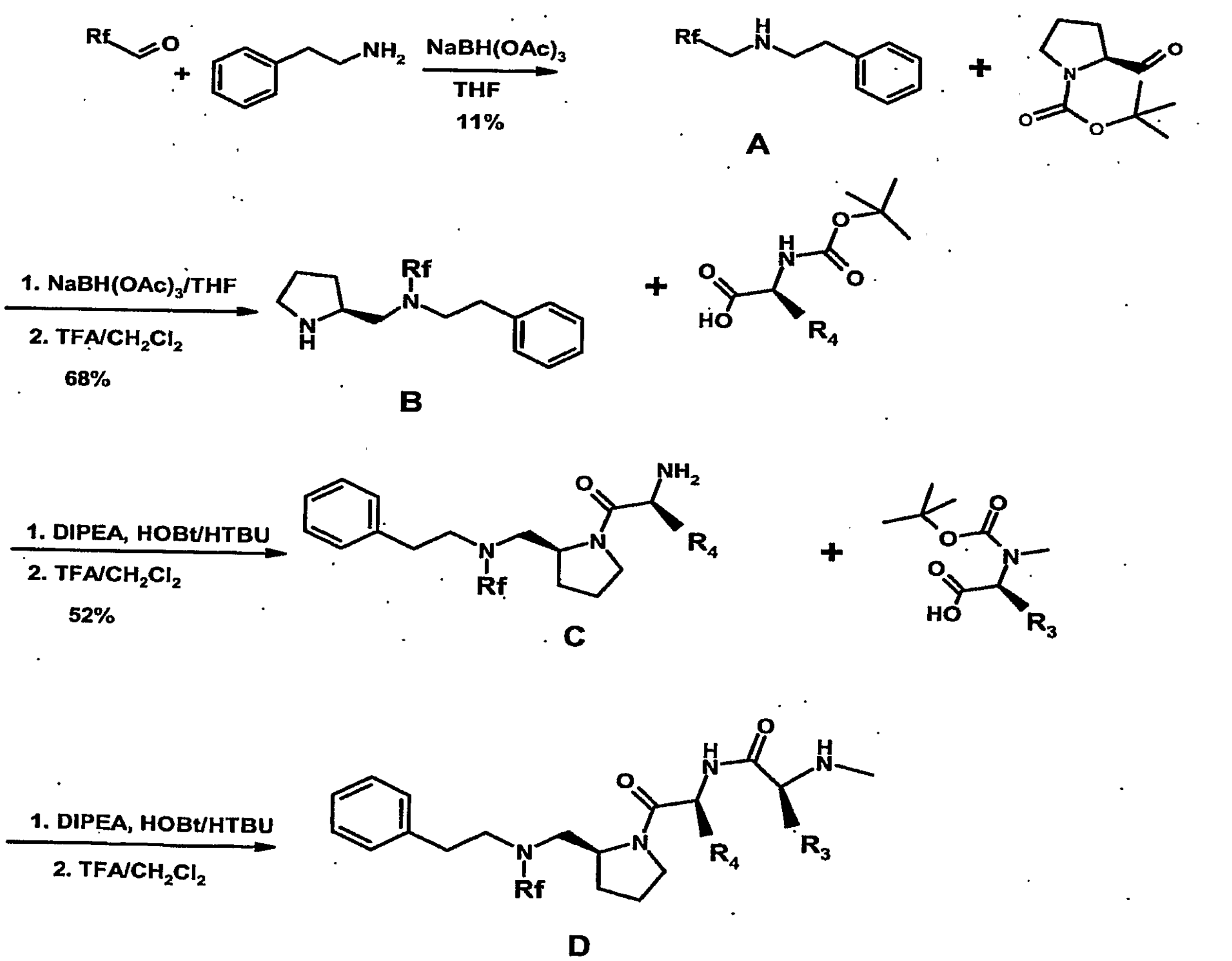
Step E: This step involves the reduction of the amide to an amine *via* standard reduction conditions employing DIBAL-H.

Step F: This step involves the removal of the benzylic protecting group using standard palladium conditions under a hydrogen atmosphere.

Step G: This step involves coupling of the scaffold with a *t*-Boc protected natural or unnatural amino acid using standard peptide coupling conditions followed by the removal of the *t*-Boc group with TFA.

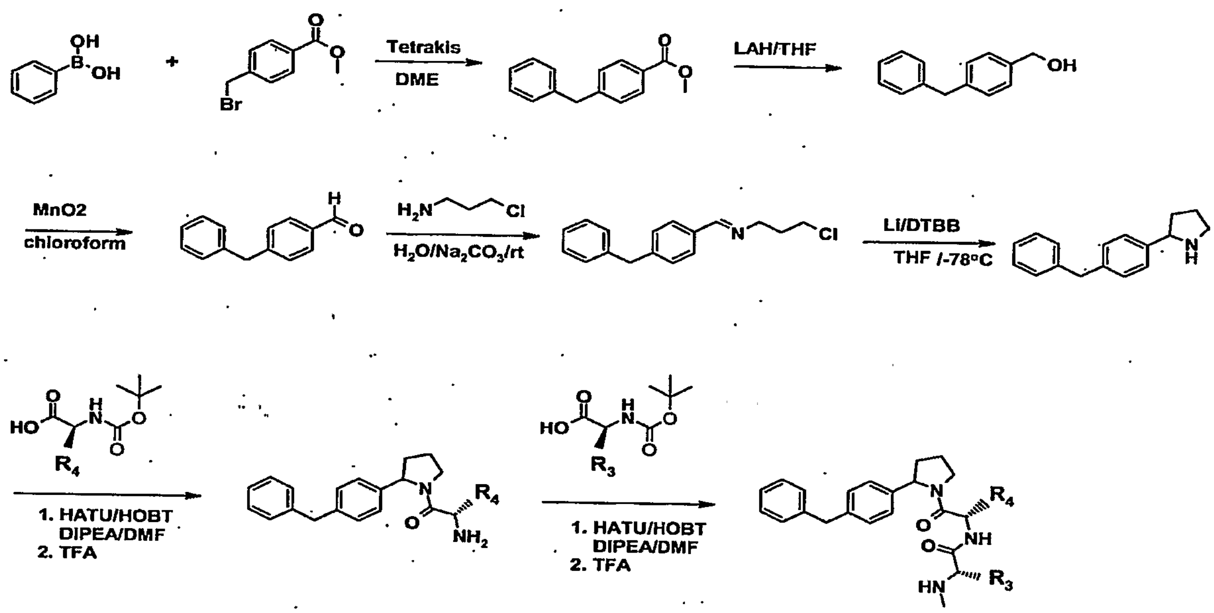
Step H: This step involves the coupling of the amine generated in the preceding step with a *t*-Boc protected or tertiary natural or unnatural amino acid using standard peptide coupling conditions followed by the removal of the *t*-Boc group with TFA if applicable. The product is then purified by high-performance liquid chromatography (HPLC).

The compounds of formula **(I)** may be prepared as depicted below in scheme 2 (for compound # **25 – 27**):



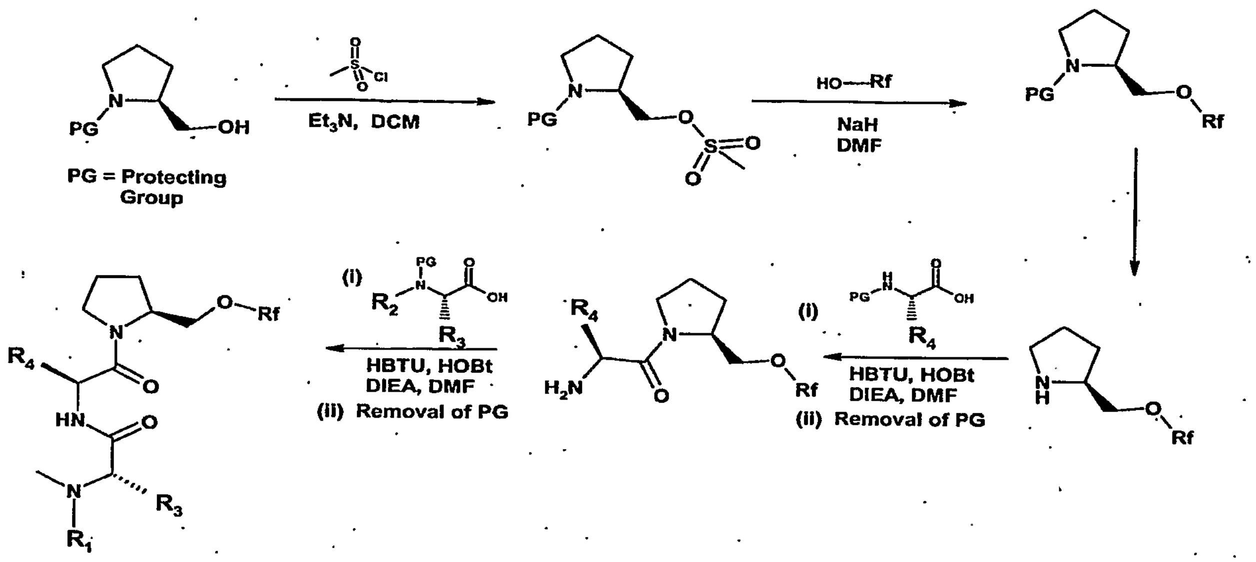
Scheme 2

The compounds of formula (**I**) may be prepared as depicted below in scheme 3 (for compound # **31 – 32**):



Scheme 3

The compounds of formula (**I**) may be prepared as depicted below in scheme 4 (for compound # **33 – 34**):



Scheme 4

Compounds 35-37 can be prepared analogously to the preparation of compounds 33-34 according to Scheme 4.

The present invention further includes pharmaceutical compositions comprising a pharmaceutically effective amount of one or more of the above-described compounds as active ingredient. Pharmaceutical compositions according to the invention are suitable for enteral, such as oral or rectal, and parenteral administration to mammals, including man, for the treatment of proliferative diseases, including tumors, especially cancerous tumors, and other cancers alone or in combination with one or more pharmaceutically acceptable carriers.

The inventive compounds are useful for the manufacture of pharmaceutical compositions having an effective amount of the compound in conjunction or admixture with excipients or carriers suitable for either enteral or parenteral application. Examples include tablets and gelatin capsules comprising the active ingredient together with (a) diluents; (b) lubricants, (c) binders (tablets); if desired, (d) disintegrants; and/or (e) absorbents, colorants, flavors and sweeteners. Injectable compositions are preferably aqueous isotonic solutions or suspensions, and

suppositories are advantageously prepared from fatty emulsions or suspensions. The compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, the compositions may also contain other therapeutically valuable substances. The compositions are prepared according to conventional mixing, granulating or coating methods, respectively, and contain preferably about 1 to 50% of the active ingredient.

Suitable formulations also include formulations for parenteral administration such as aqueous and non-aqueous sterile injection solutions which may contain antioxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example, sealed ampules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

The pharmaceutical composition contains a pharmaceutically effective amount of the present active agent along with other pharmaceutically acceptable excipients, carriers, fillers, diluents and the like. The term therapeutically effective amount as used herein indicates an amount necessary to administer to a host to achieve a therapeutic result, especially an anti-tumor effect, e.g., inhibition of proliferation of malignant cancer cells, benign tumor cells or other proliferative cells.

As discussed above, the compounds of the present invention are useful for treating proliferative diseases. Thus, the present invention further relates to a method of treating a proliferative disease which comprises administering a therapeutically effective amount of a compound of the invention to a mammal, preferably a human, in need of such treatment.

A proliferative disease is mainly a tumor disease (or cancer) (and/or any metastases). The inventive compounds are particularly useful for treating a tumor which is a breast cancer, genitourinary cancer, lung cancer, gastrointestinal cancer, epidermoid cancer, melanoma, ovarian cancer, pancreas cancer, neuroblastoma, head and/or neck cancer or bladder cancer, or in a broader sense renal, brain or gastric cancer; in particular (i) a breast tumor; an epidermoid tumor, such as an epidermoid head and/or neck tumor or a mouth tumor; a lung tumor, for example a small cell or non-small cell lung tumor; a gastrointestinal tumor, for example, a colorectal tumor; or a genitourinary tumor, for example, a prostate tumor (especially a hormone-refractory prostate tumor); or (ii) a proliferative disease that is refractory to the treatment with other chemotherapeutics; or (iii) a tumor that is refractory to treatment with other chemotherapeutics due to multidrug resistance.

In a broader sense of the invention, a proliferative disease may furthermore be a hyperproliferative condition such as leukemias, hyperplasias, fibrosis (especially pulmonary, but also other types of fibrosis, such as renal fibrosis), angiogenesis, psoriasis, atherosclerosis and smooth muscle proliferation in the blood vessels, such as stenosis or restenosis following angioplasty.

Where a tumor, a tumor disease, a carcinoma or a cancer are mentioned, also metastasis in the original organ or tissue and/or in any other location are implied alternatively or in addition, whatever the location of the tumor and/or metastasis.

The inventive compound is selectively toxic or more toxic to rapidly proliferating cells than to normal cells, particularly in human cancer cells, e.g., cancerous tumors, the compound has significant antiproliferative effects and promotes differentiation, e.g., cell cycle arrest and apoptosis.

The compounds of the present invention may be administered alone or in combination with other anticancer agents, such as compounds that inhibit tumor

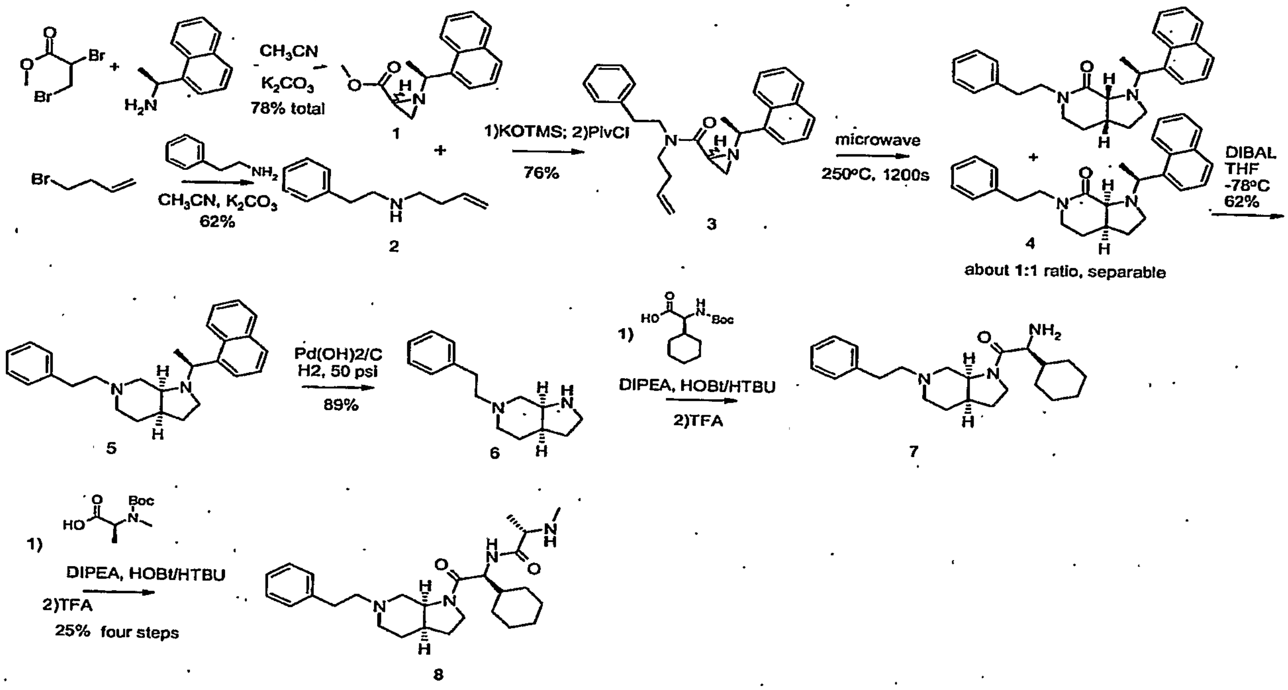
angiogenesis, for example, the protease inhibitors, epidermal growth factor receptor kinase inhibitors, vascular endothelial growth factor receptor kinase inhibitors and the like; cytotoxic drugs, such as antimetabolites, like purine and pyrimidine analog antimetabolites; antimitotic agents like microtubule stabilizing drugs and antimitotic alkaloids; platinum coordination complexes; anti-tumor antibiotics; alkylating agents, such as nitrogen mustards and nitrosoureas; endocrine agents, such as adrenocorticosteroids, androgens, anti-androgens, estrogens, anti-estrogens, aromatase inhibitors, gonadotropin-releasing hormone agonists and somatostatin analogues and compounds that target an enzyme or receptor that is overexpressed and/or otherwise involved a specific metabolic pathway that is upregulated in the tumor cell, for example ATP and GTP phosphodiesterase inhibitors, histone deacetylase inhibitors, protein kinase inhibitors, such as serine, threonine and tyrosine kinase inhibitors, for example, Abelson protein tryosine kinase and the various growth factors, their receptors and kinase inhibitors therefore, such as, epidermal growth factor receptor kinase inhibitors, vascular endothelial growth factor receptor kinase inhibitors, fibroblast growth factor inhibitors, insulin-like growth factor receptor inhibitors and platelet-derived growth factor receptor kinase inhibitors and the like; methionine aminopeptidase inhibitors, proteasome inhibitors, and cyclooxygenase inhibitors, for example, cyclooxygenase-1 or –2 inhibitors.

The present invention further relates to a method of promoting apoptosis in rapidly proliferating cells, which comprises contacting the rapidly proliferating cells with an effective apoptosis promoting amount of a non-naturally-occurring compound that binds to the Smac binding site of XIAP and/or cIAP proteins. Preferably, the non-naturally-occurring compound a compound of present formula I or IV.

The following examples are intended to illustrate, but not further limit, the invention.

Example 1

Compound **8** according to Formula I is prepared according to the procedure set forth in Scheme 5.



Scheme 5

1-(1-Naphthalen-1-yl-ethyl)-aziridine-2-carboxylic acid methyl ester (1). To a solution of (S)-(-)-1-(1-naphthyl)ethylamine (20.8 g, 120 mmol) in acetonitrile (HPLC grade, 600 mL) is added K_2CO_3 (52.7 g, 360 mmol) and methyl 2,3-dibromopropionate (30 g, 120 mmol). The solution is stirred overnight at room temperature. The solution is evaporated to dryness, then H_2O/EtOAc (1:1) (600 mL) is added, and the mixture is extracted with EtOAc (4x100 mL). The organic extracts are combined, dried and concentrated under vacuum. The residue is purified by flash chromatography (silica gel; Hexane/EtOAc 1:2) to provide 24 g (78%) of the title compound as a mixture of two diastereomers in an equimolecular ratio. $M+H^+$= 256.10.

But-3-enyl-phenethyl-amine (2). To a solution of 2-phenylethylamine (72 mL, 570 mmol) is added K_2CO_3 (82 g, 570 mmol) and 4-bromo-1-butene (25 g, 185 mmol).

The solution is stirred overnight at room temperature. The solution is evaporated to dryness and H_2O/EtOAc (1:1) (600 mL) is added. The mixture is extracted with EtOAc (4x150 mL). The organic extracts are combined, dried and concentrated under vacuum. The residue is purified by flash chromatography (silica gel; Hexane/EtOAc 1:8) to provide 20 g (62%) of the title compound. $M+H^+$= 176.10.

1-(1-Naphthalen-1-yl-ethyl)-aziridine-2-carboxylic acid but-3-enyl-phenethyl-amide (3). To a solution of **1** (12.6 g, 49.75 mmol) in THF (200 mL) is added KOTMS (6.38 g, 49.75 mmol). The mixture is stirred overnight at room temperature. The mixture is concentrated and the residue dissolved in dichloromethane (200 mL) and cooled to 0° C. Trimethylacetyl chloride (5.94 g, 49.25 mmol) is added slowly and the mixture is warmed to room temperature over 2 hours. The mixture is cooled to -78° C, **2** (8.63 g, 49.25 mmol) is added and stirring continued at -78°C for 1.5 h. Saturated sodium bicarbonate (100mL) is added and the mixture is allowed to warm to rt. The mixture is extracted with EtOAc (4x100 mL) and the organic extracts are combined, dried and concentrated under vacuum. The residue is purified by flash chromatography (silica gel; Hexane/EtOAc 1:8) to provide 15 g (76%) of the title compound as a mixture of two diastereomers in an equimolecular ratio. $M+H^+$= 399.37.

1-(1-Naphthalen-1-yl-ethyl)-6-phenethyl-octahydro-pyrrolo[2,3-c]pyridin-7-one (4). A solution of **3** (15 g, 58.7 mmol) in o-dichlorobenzene (100 mL) is heated at 250° C for 1200 s in a microwave reactor. The mixture is purified by flash chromatography (silica gel; Hexane/EtOAc 1:1; second spot) to provide 5 g (33%) of the title compound as an enantiomerically pure compound. $M+H^+$= 399.32.

1-(1-Naphthalen-1-yl-ethyl)-6-phenethyl-octahydro-pyrrolo[2,3-c]pyridine (5). To a solution of **4** (4.8 g, 12 mmol) in THF (100 mL) is added slowly 1 M DIBAL in toluene, (50 mL, 50 mmol) at -78°C. The mixture is stirred at room temperature for 1 hour and quenched with 20 mL of water. The solvent is evaporated, the residue is diluted with 100 mL of 1:1 saturated Rochells salt/15% NaOH, and this extracted

with EtOAc (4x50 mL). The organic extracts are combined, dried and concentrated under vacuum. The residue is purified by flash chromatography (silica gel; Hexane/EtOAc 1:9) to provide 2.3 g (48%) of the title compound. $M+H^+$= 385.26.

6-Phenethyl-octahydro-pyrrolo[2,3-c]pyridine (6). To a solution of **5** (2.3 g, 6 mmol) in $MeOH/CH_2Cl_2$ (1:1; 200 mL) is added $Pd(OH)_2$ (300 mg). The mixture is agitated under 50psi. hydrogen atmosphere for 10 h. The mixture is filtered through a celite pad, the filtrate is concentrated and the residue is used directly in the next step without further purification. $M+H^+$= 231.17.

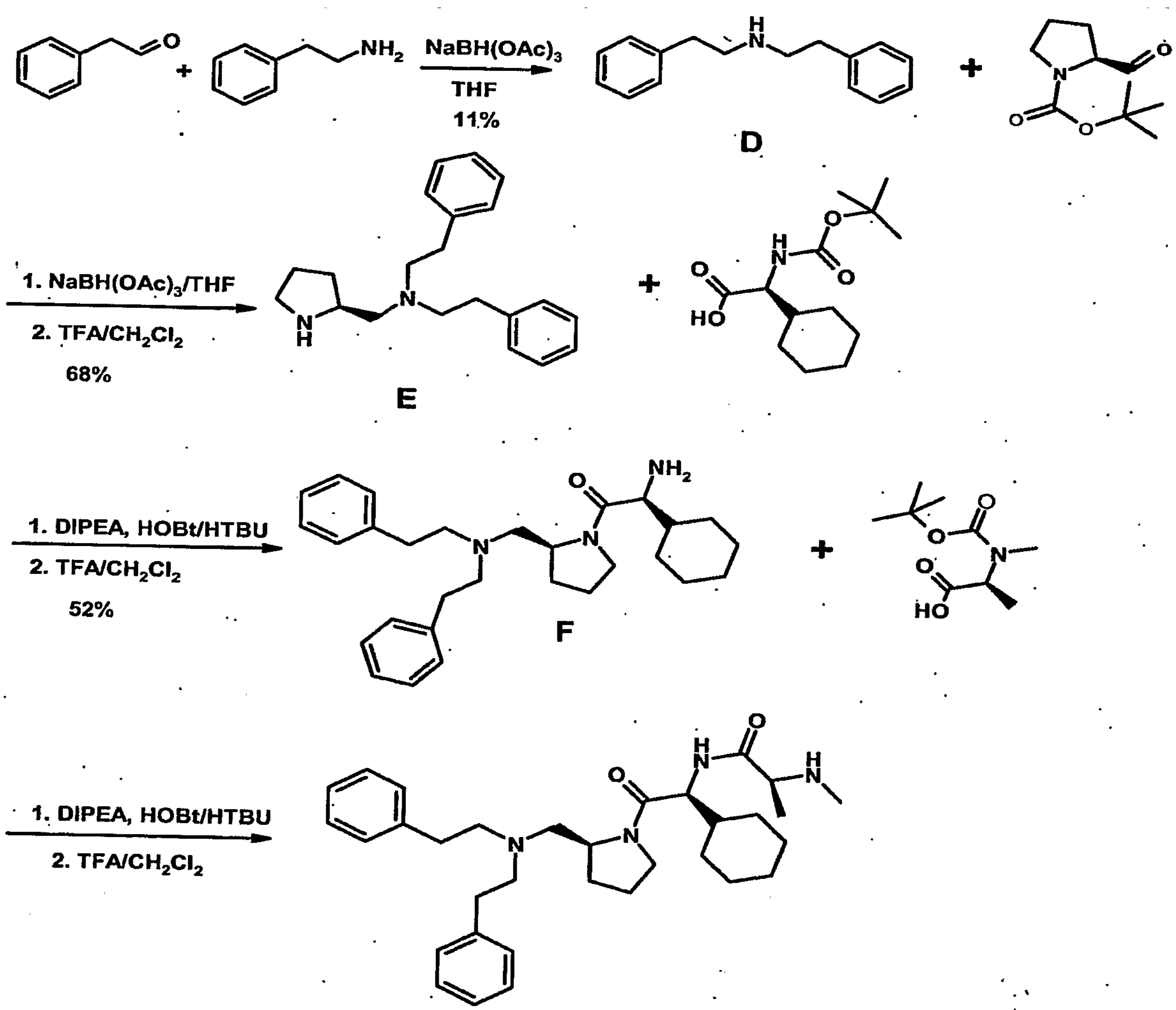
Compound (7). To a solution of **6** in dichloromethane (25 mL) is added sequentially diisopropylethylamine (4.17 mL, 24 mmol), *t*-Boc-L-cyclohexylglycine (1.54 g, 6 mmol), and a solution of 0.45 M HOBt/HBTU in DMF (16 mL, 7.19 mmol). The mixture is stirred overnight at room temperature, then diluted with EtOAc (200 mL) and washed sequentially with 1 M aq. citric acid (50 mL), water (50 mL), aq. Sat. $NaHCO_3$ (50 mL) and brine (2x50 mL). The organic layer is dried and concentrated under vacuum. The residue is purified by flash chromatography (silica gel; Hexane/EtOAc 1:9) to provide a yellow oil. The yellow oil is dissolved in dichloromethane (20 mL), TFA (10 mL) is added and the mixture is stirred at room temperature for 3 h. The mixture is concentrated and the residue is dissolved in dichloromethane (100 mL) and neutralized with saturated sodium bicarbonate. The solution is extracted with dichloromethane (3x50 mL). The organic extracts are combined, dried and concentrated under vacuum to provide1.75 g (79% two steps) of the title compound which is used in next step without further purification or characterization.

Compound (8). To a solution of **7** (1.75 g, 4.74 mmol) in dichloromethane (25 mL) is added sequentially diisopropylethylamine (3.30 mL, 19 mmol), *t*-Boc-*N*-methyl-L-alanine (0.97 g, 4.74 mmol), and a solution of 0.45 M HOBt/HBTU in DMF (13 mL, 5.691 mmol). The mixture is stirred overnight at room temperature. The mixture is diluted with EtOAc (200 mL) and washed sequentially with 1 M citric acid (50 mL),

water (50 mL), aq. Sat. $NaHCO_3$ (50 mL) and brine (2x50 mL). The organic layer is dried and concentrated under vacuum. The residue is dissolved in dichloromethane (20 mL), TFA (10 mL) is added and the mixture is stirred at room temperature for 3 hours. The mixture is concentrated and the residue is dissolved in dichloromethane (100 mL) and neutralized with saturated sodium bicarbonate. The solution is extracted with dichloromethane (3x50 mL). The organic extracts are combined, dried and concentrated under vacuum. The residue is purified by HPLC (C-18 silica gel, 20% CH_3CN/H_2O in 0.5%TFA) to provide1 g (36% two steps) of the title compound as TFA salt. $M+H^+$= 455.39.

The title compound **25** (Formula 1) is prepared according to the procedure set forth in Scheme 6.

Synthesis of compound 25



25

Scheme 6

Diphenethylamine (D). To a solution of phenylacetaldehyde (6.0 g, 50 mmol) and 2-phenylethylamine in THF (200 mL) is added sodium triacetoxy-borohydride drop wise. The solution is stirred under nitrogen overnight at room temperature. The solution is quenched with aq. saturated sodium bicarbonate (200 mL), and extracted with EtOAc (4x100 mL). The organic extracts are combined, dried and concentrated

under vacuum. The residue is purified by flash chromatography (silica gel; EtOAc/ MeOH 9:1) to provide 1.25 g (11%) of the compound **D** as a clear oil. $M+H^+= 226.10$.

Diphenethyl-(S)-1-pyrrolidin-2-ylmethyl-amine (E). To a solution of (S)-2-Formyl-pyrrolidine-1-carboxylic acid tert-butyl ester (1.0 g, 5.0 mmol) and **D** (1.125 g, 5.0 mmol) in THF (40 mL) is added sodium triacetoxyborohydride drop wise. The solution is stirred under nitrogen overnight at room temperature. The solution is quenched with aq. saturated sodium bicarbonate (40 mL). The mixture is extracted with EtOAc (4x50 mL). The organic extracts are combined, dried and concentrated under vacuum. The residue is purified by flash chromatography (silica gel; Hexane/EtOAc 4:1) to provide a yellow oil. The yellow oil is dissolved in dichloromethane (20 mL), TFA (10 mL) is added and the mixture is stirred at room temperature for 3 h. The mixture is concentrated and the residue is dissolved in dichloromethane (100 mL) and neutralized with saturated sodium bicarbonate. The solution is extracted with dichloromethane (3x50 mL). The organic extracts are combined, dried and concentrated under vacuum to provide1.04 g (68% two steps) of the title compound **E** which is used in the next step without further purification or characterization.

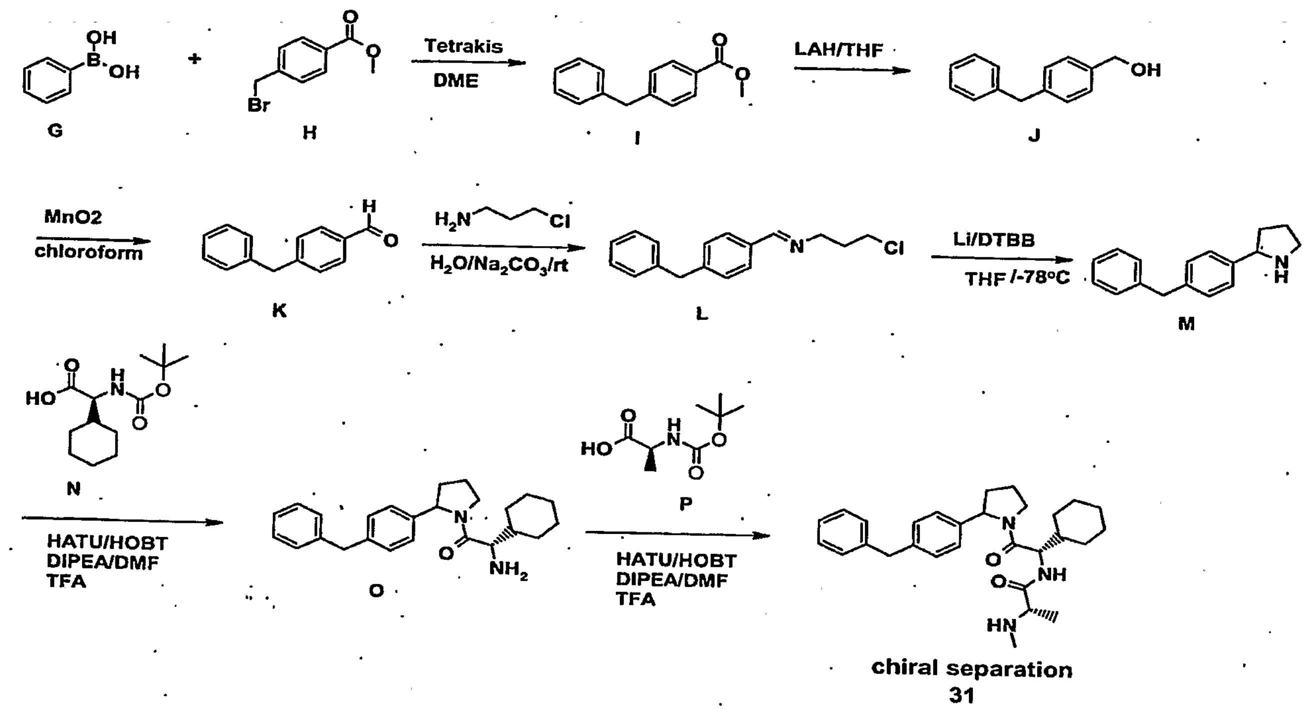
Compound (F). To a solution of *t*-Boc-L-cyclohexylglycine (0.868 g, 3.38 mmol) in DMF (20 mL) is added diisopropylethylamine (1.83 mL, 16.9 mmol). The mixture is stirred for 20 minutes at room temperature. Then a solution of **E**, HOBt (516 mg, 3.82 mmol) and HBTU (1.448 g, 3.82 mmol) in DMF (30 mL) is added. The mixture is stirred overnight at room temperature, and then diluted by ether (200 mL) and washed sequentially with aq. 1M citric acid (50 mL), water (50 mL), satd. aq. $NaHCO_3$ (50 mL) and brine (2x50 mL). The organic extract is dried and concentrated under vacuum. The residue is purified by flash chromatography (silica gel; Hexane/EtOAc 2:3) to provide a yellow oil. The yellow oil is dissolved in dichloromethane (20 mL), TFA (10 mL) is added and the mixture is stirred at room temperature for 3 hours. The mixture is concentrated and the residue is dissolved in dichloromethane (100 mL) and neutralized with saturated sodium bicarbonate. The

solution is extracted with dichloromethane (3x50 mL). The organic extracts are combined, dried and concentrated under vacuum to provide 780 mg (52% two steps) of the title compound **F** which is used in the next step without further purification or characterization.

Compound 25. To a solution of *t*-Boc-*N*-methyl-L-alanine (354 mg, 1.75 mmol) in DMF (20 mL) is added diisopropylethylamine (0.938 mL, 8.75 mmol). The mixture is stirred for 20 minutes at room temperature. Then a solution of **F**, HOBt (267 mg, 1.98 mmol) and HBTU (751 mg, 1.98 mmol) in DMF (30 mL) is added. The mixture is stirred for 3 h at room temperature, and then diluted by ether(200 mL) and washed sequentially with 1 M citric acid (50mL), water (50 mL), satd. aq. $NaHCO_3$ (50 mL) and brine (2x50 mL). The organic extract is dried and concentrated under vacuum. The residue is dissolved in dichloromethane (20 mL) and TFA (10 mL) is added. The mixture is stirred at room temperature for 3 h and concentrated. The resulting residue is dissolved in dichloromethane (100 mL) and neutralized with saturated sodium bicarbonate. The solution is extracted with dichloromethane (3x50 mL). The organic extracts are combined, dried and concentrated under vacuum. Portion of the residue is purified by HPLC (C-18 silica gel, 30% CH_3CN/H_2O in 0.5%TFA) to provide 120 mg of the title compound **25** as TFA salt. $M+H^+ = 533.47$.

The title compound **31** (Formula 1) is prepared according to the procedure set forth in Scheme 7.

Synthesis of compound 31



Scheme 7

Compound I. Compounds **G** (122 mg,1 mmole) and **H** (226 mg,1 mmole) are dissolved in 5 mL DME. To this a mixture of 1 mL 2 N aq. Na_2CO_3 and 50 mg **Tetrakis** is added. The resulting mixture is degassed for 5 minutes, stirred at 90 °C for 6 h, cooled down to room temperature, and concentrated. The residue is purified by flash chromatography (ethyl acetate/hexane) to provide **I** as an amber oil (204 mg, 90%). The crude product is used directly in next reaction without further purification or characterization.

Compound J. LAH (38 mg) is added to a solution of **I** (226 mg,1 mmole) in 5 mL THF 0 °C. The temperature of the mixture is allowed to warm to room temperature and further stirred overnight. The reaction is quenched by following the Fisher method, filtered and concentrated to provide **J** as a colorless oil (183 mg, 92%) and is used directly in next reaction without further purification or characterization.

Compound K. The suspension of compound **J** (198 mg, 1 mmole) and MnO_2 (870 mg, 10 mmole) in 15 mL chloroform is stirred overnight. Filtering and concentration yielded product **K** as a colorless oil (192 mg, 98%).
^1H NMR ($CDCl_3$) δ 9.96 (s, 1H), 7.72 (s,2H), 7.47 (s, 2H), 7.15-7.35 (m,5H), 4.07 (s, 2H)

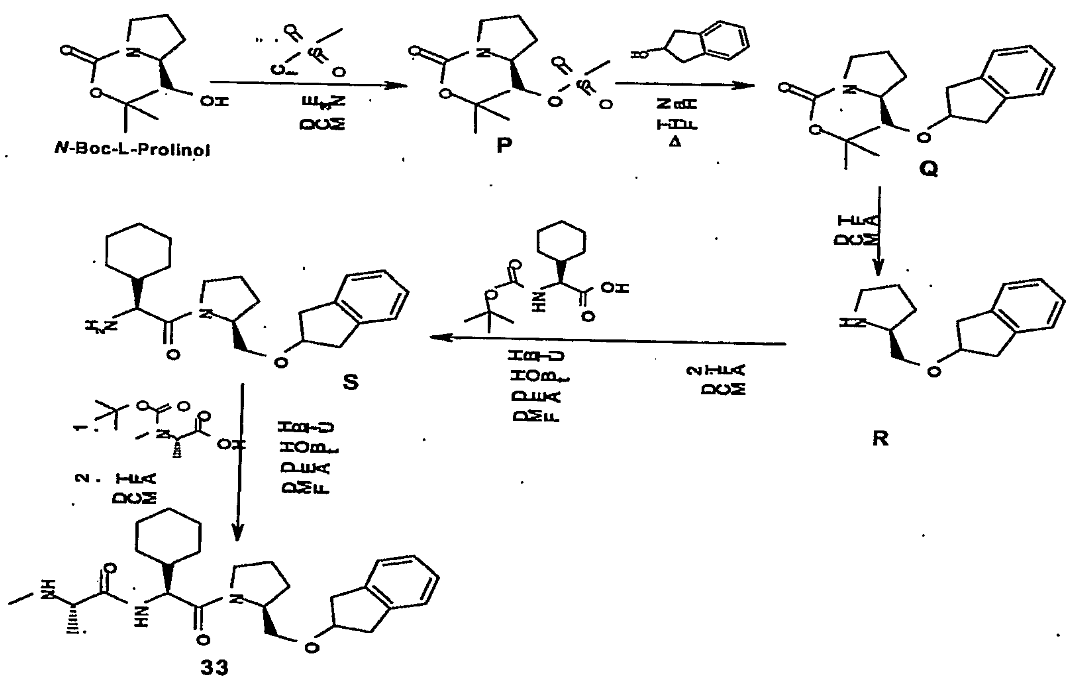
Compound L. A mixture of 3-chloropropylamine hydrochloride (140 mg, 1.1 mmol), aldehyde **K** (196 mg, 1.0 mmol), and sodium carbonate (212 mg, 2 mmol) in water (10 mL) is stirred overnight at room temperature. The resulting solution is extracted with ethyl acetate (3 x 20 mL), separated, dried over Na_2SO_4 and evaporated in vacuum (15 Torr) to give an essentially pure oily residue (270 mg) which is used for the next reaction without further purification. (M $+H^+$ 272, calc. 272)

Compound M. Imine **L** (271 mg,1 mmol) is added to a blue suspension of lithium powder (75 mg, 10 mmol) and a catalytic amount of DTBB (30 mg, 0.10 mmol; 5% molar) in THF (5 mL) at -78 °C. The resulting mixture is stirred for 2 h at same temperature. Reaction is quenched with water (20 mL) allowing the temperature to rise to 20 °C. The resulting solution is purified by successively acid-base extraction with 2 M hydrochloric acid (3 x 15 mL) and 4 M sodium hydroxide (3 x 20 mL). The final solution is extracted with ethyl acetate (3 x 20 mL), separated, dried over Na_2SO_4 and evaporated to give pure compound **M**, (214 mg, 90%); (M $+H^+$ 238, calc. 238)

Compound O. A mixture of compound **M** (237 mg,1 mmole) , compound **N** (257 mg,1 mmole), HBTU (460 mg,1.2 mmole), HOBT (170 mg, 1.1 mmole), DIPEA (512 mg, 3 mmole) and 5 mL DMF is stirred overnight. The mixture is diluted with ether (25 mL), washed with water, brine, dried over $MgSO_4$, filtered, and concentrated. The resulting residue is treated with 2 mL of CH_2Cl_2/TFA (1/1), stirred for 2 h, concentrated to provided product **O** as a pale yellow solid (320 mg, 85%); (M $+H^+$ 377, calc. 377).

Compound 31. A mixture of compound **O** (376 mg, 1 mmole), *t*-Boc-*N*-methylalanine **P** (203 mg,1 mmole), HBTU (460 mg,1.2 mmole), HOBT (170 mg, 1.1 mmole), DIPEA (512 mg, 3 mmole) and 5 mL DMF is stirred overnight. The mixture is diluted with ether (25 mL), washed with water, brine, dried over $MgSO_4$, filtered, and concentrated. The resulting residue is treated with 2 mL of CH_2Cl_2 /TFA (1/1), stirred for 2 h and concentrated under vacuum. Column chromatography provided compound **31** as a pale yellow solid, (397 mg, 86%). (M +H^+ 462, calc. 462).

The title compound **33** (Formula I) is prepared according to the procedure set forth in Scheme 8.



Scheme 8

(S)-2-Methanesulfonyloxymethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester, (P). A flame dried flask charged with (S)-2-Hydroxymethyl-pyrrolidine-1-

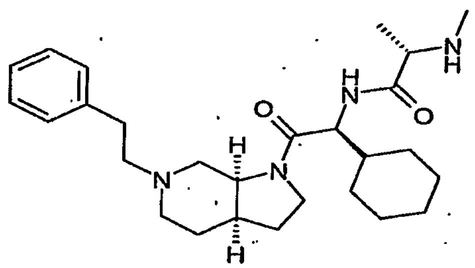
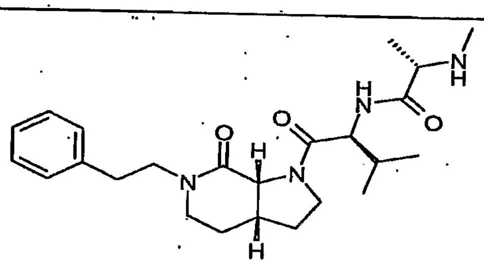
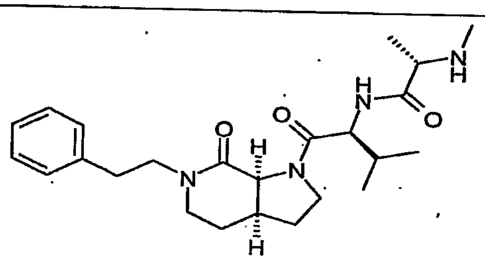
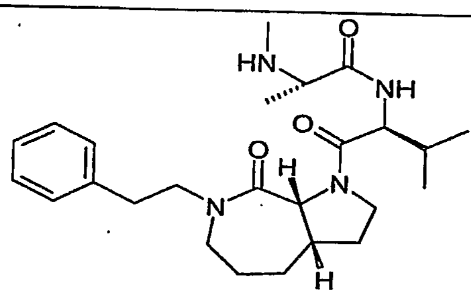
carboxylic acid *tert*-butyl ester (1 g, 5 mmol), dichloromethane (DCM) (20 mL) and triethylamine (0.70 mL, 5.2 mmol) is cooled to 0°C under N_2 is added a solution of methanesulfonychloride (0.38 mL, 5 mmol) in DCM (5 mL) dropwise over 10 minutes. The reaction is stirred for 1 hour . After addition of DCM (100 mL), the reaction mixture is washed with brine, dried and concentrated *in vacuo*. The residue is purified by chromatography on SiO_2 (5% EtOAc/Hexanes) to give 1.38 g of methanesulfonate ester (**P**) as a clear colorless oil: LCMS (ES) 280.10 (MH^+).

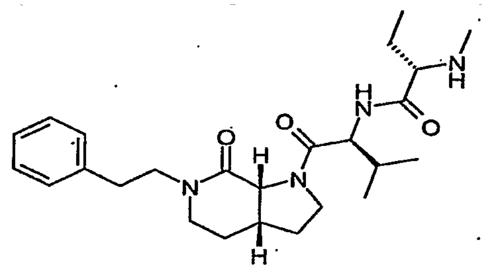
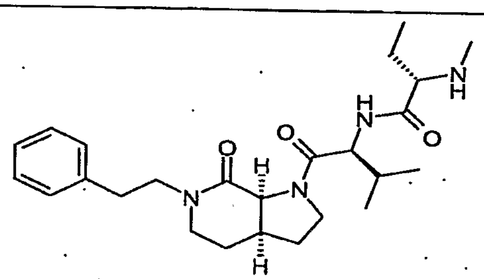
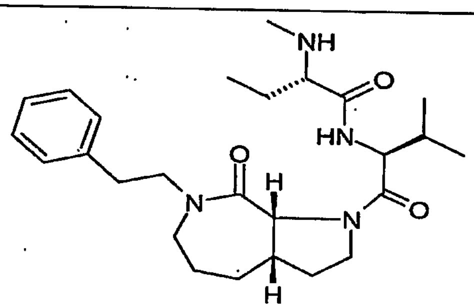
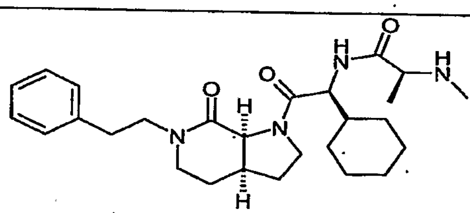
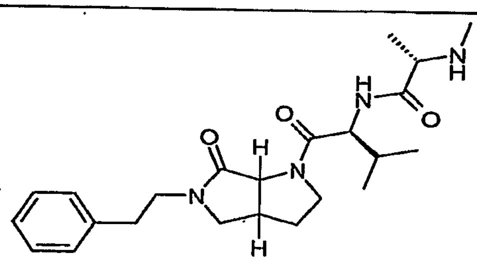
(S)-2-(Indan-2-yloxymethyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester, (Q). Sodium hydride (60%) (0.6 g, 14.4 mmol) is added to a flame dried flask charged with indan-2-ol (0.965 g, 7.2 mmol) and N,N'-dimethylformamide (DMF) (20 mL), cooled to 0°C under N_2 and stirred for 30 minutes. A solution of (S)-2-Methanesulfonyloxymethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (**P**) (1 g, 3.6 mmol) in DMF (5 mL) is added dropwise to the reaction mixture in such a manner as to maintain 0°C. The reaction is stirred at 60 °C for one hour, cooled to 0°C, quenched with brine, diluted with EtOAc, washed repeatedly with brine (6X), dried and concentrated *in vacuo*. The residue is purified by chromatography on SiO_2 (5% EtOAc/Hexanes) to give 0.20 g of indanyl ether (**Q**) as a clear colorless oil: LCMS (ES) 340.17 (MNa+).

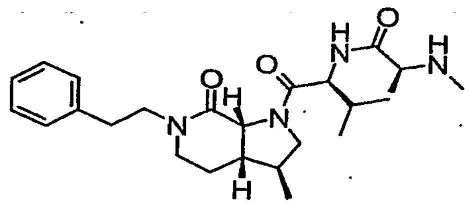
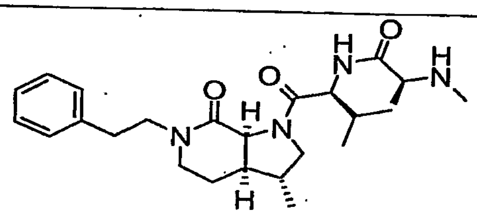
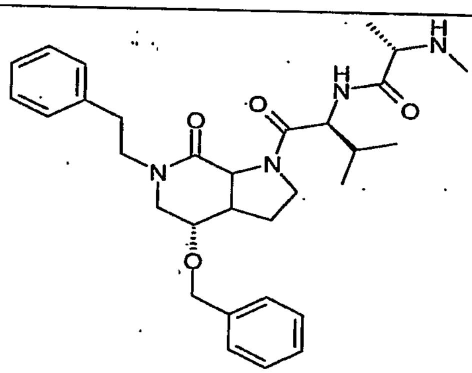
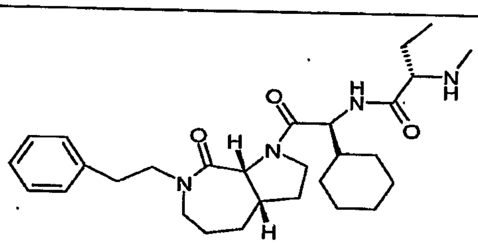
(S)-N-{(S)-1-Cyclohexyl-2-[(S)-2-(indan-2-yloxymethyl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methylamino-propionamide, (33). ((S)-1-{(S)-1-Cyclohexyl-2-[(S)-2-(indan-2-yloxymethyl)-pyrrolidin-1-yl]-2-oxo-ethylcarbamoyl}-ethyl)-methyl-carbamic acid *tert*-butyl ester (**Q**) (0.54 g, 1 mmol) is dissolved in DCM (8mL) and treated with trifluoroacetic acid (4 mL) for 45 minutes. The reaction mixture is concentrated in vacuo, purified by preparative reverse-phase hplc to give 0.096 g of the methylamine (**33**) as a clear gum: LCMS (ES) 442.26 (MH+).

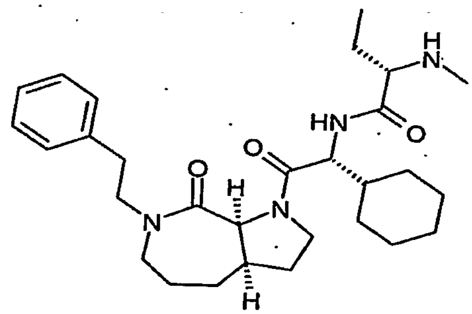
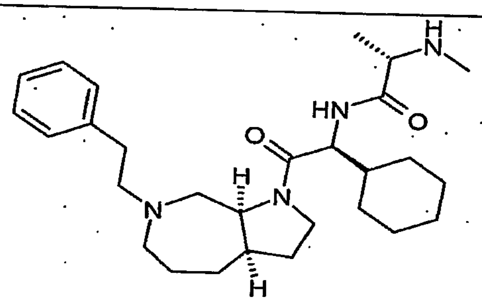
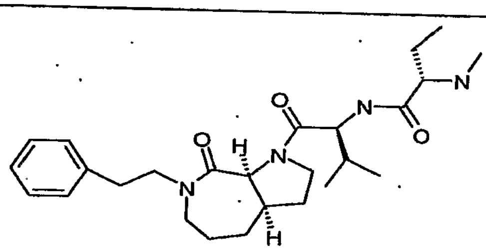
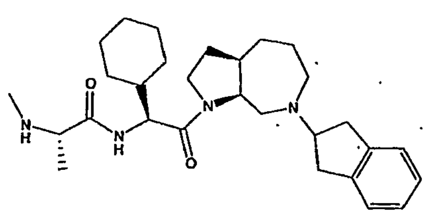
Examples 8 - 37

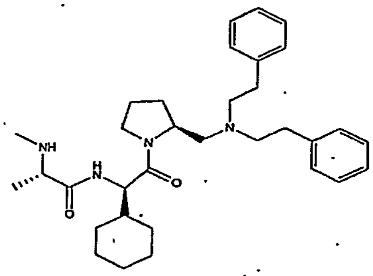
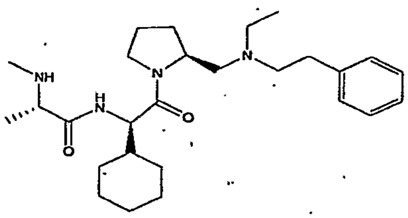
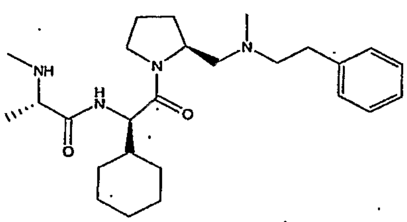
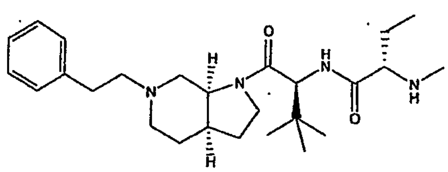
The following compounds are prepared by methods analogous to those described herein utilizing analogous starting materials:

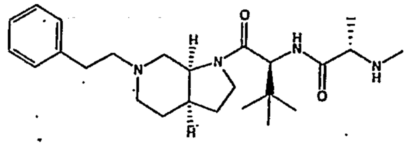
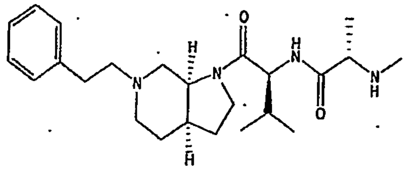
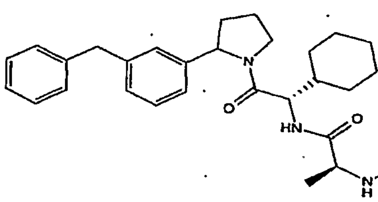
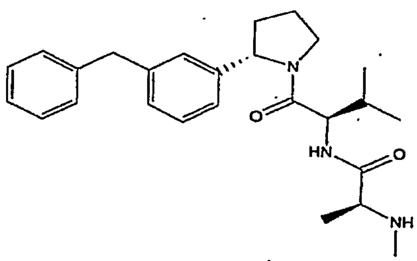
Compound Structure	Example Number
	Example 8 MS ESI 455.34 $(M+H)^+$
	Example 9 MS ESI 429.46 $(M+H)^+$
	Example 10 MS ESI 429.46 $(M+H)^+$
	Example 11 MS ESI 443.46 $(M+H)^+$

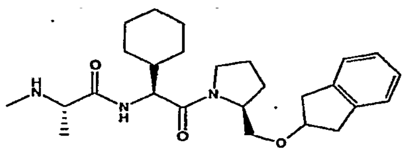
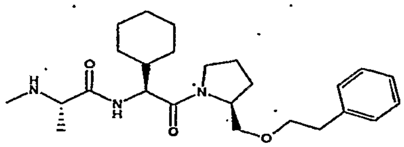
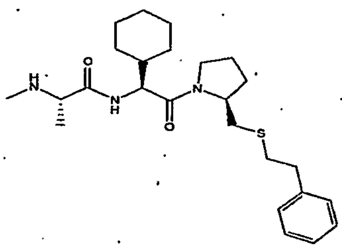
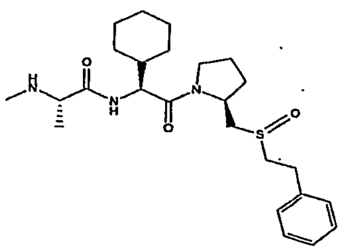
	Example 12 MS ESI 443.47 $(M+H)^+$
	Example 13 MS ESI 443.48 $(M+H)^+$
	Example 14 MS ESI 457.27 $(M+H)^+$
	Example 15 MS ESI 469.23 $(M+H)^+$
	Example 16 MS ESI 415.26 $(M+H)^+$

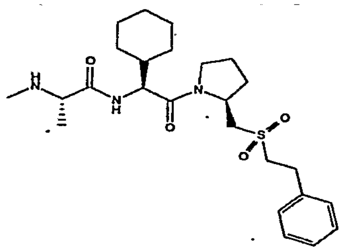
	Example 17 MS ESI 443.19 (M+H)$^+$
	Example 18 MS ESI 443.19 (M+H)$^+$
	Example 19 MS ESI 535.33 (M+H)$^+$
	Example 20 MS ESI 497.35 (M+H)$^+$

	Example 21 MS ESI 497.35 $(M+H)^+$
	Example 22 MS ESI 469.36 $(M+H)^+$
	Example 23 MS ESI 457.6 $(M+H)^+$
	Example 24 MS ESI 481.7 $(M+H)^+$

	Example 25 MS ESI 533.5 $(M+H)^+$
	Example 26 MS ESI 457.43 $(M+H)^+$
	Example 27 MS ESI 443.23 $(M+H)^+$
	Example 28 MS ESI 442.65 $(M+H)^+$

	Example 29 MS ESI 428.62 $(M+H)^+$
	Example 30 MS ESI 414.30 $(M+H)^+$
	Example 31 MS ESI 462.0 $(M+H)^+$
	Example 32 MS ESI 422.1 $(M+H)^+$

	Example 33 MS ESI 442.26 $(M+H)^+$
	Example 34 MS ESI 430.28 $(M+H)^+$
	Example 35 MS ESI 446.6 $(M+H)^+$
	Example 36 MS ESI 462.6 $(M+H)^+$

	Example 37 MS ESI 478.7 $(M+H)^+$

In order to measure the ability of the inventive compounds to bind the BIR3 peptide binding pocket an ELISA and a cell based assays are utilized.

Elisa

Compounds are incubated with GST-BIR3 fusion protein and biotinylated SMAC peptide (AVPFAQK) in stretavidin-coated 96 well plates. For XIAP BIR3 Smac Elisa, a GST-BIR3 fusion containing amino acids 248-358 from XIAP is used. For CIAP1 BIR3 Smac Elisa, a GST-BIR3 fusion containing amino acids 259-364 from CIAP1 is used. Following a 30 minute incubation, wells are extensively washed. The remaining GST-BIR3 fusion protein is monitored by ELISA assay involving first, incubation with goat anti-GST antibodies followed by washing and incubation with alkaline phosphatase conjugated anti-goat antibodies. Signal is amplified using Attophos (Promega) and read with Cytoflour Ex 450nm/40 and Em 580nm. IC_{50}s correspond to concentration of compound which displaces half of GST-BIR3 signal. The IC_{50} for non-biotinylated Smac is 400 nM. The IC_{50} values of compounds listed in Table 1 in the described ELISA assays ranged from 0.005 – 10 μM.

Cell Proliferation Assay

The ability of compounds to inhibit tumor cell growth *in vitro* is monitored using the CellTiter 96® AQ_{ueous} Non-Radioactive Cell Proliferation Assay (Promega). This assay is composed of solutions of a novel tetrazolium compound [3-(4,5-

dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H- tetrazolium, inner salt; MTS] and an electron coupling reagent (phenazine methosulfate) PMS. MTS is bioreduced by cells into a formazan product, the absorbance of which is measured at 490nm. The conversion of MTS into the aqueous soluble formazan product is accomplished by dehydrogenase enzymes found in metabolically active cells. The quantity of formazan product as measured by the amount of 490nm absorbance is directly proportional to the number of living cells in culture. The IC_{50} values of compounds listed in Table 1 in the described cell assays ranged from 0.005 – 50 μM.

Example 38

Tablets 1 comprising compounds of the formula (I)

Tablets, comprising, as active ingredient, 50 mg of any one of the compounds of formula (I) mentioned in the preceding Examples **8-37** of the following composition are prepared using routine methods:

Composition:	
Active Ingredient	50 mg
Wheat starch	60 mg
Lactose	50 mg
Colloidal silica	5 mg
Talcum	9 mg
Magnesium stearate	1 mg
Total	175 mg

Manufacture: The active ingredient is combined with part of the wheat starch, the lactose and the colloidal silica and the mixture pressed through a sieve. A further part of the wheat starch is mixed with the 5-fold amount of water on a water bath to form a paste and the mixture made first is kneaded with this paste until a weakly plastic mass is formed.

The dry granules are pressed through a sieve having a mesh size of 3 mm, mixed with a pre-sieved mixture (1 mm sieve) of the remaining corn starch, magnesium stearate and talcum and compressed to form slightly biconvex tablets.

Example 39

Tablets 2 comprising compounds of the formula (I)

Tablets, comprising, as active ingredient, 100 mg of any one of the compounds of formula (I) of Examples **8-37** are prepared with the following composition, following standard procedures:

Composition:	
Active Ingredient	100 mg
Crystalline lactose	240 mg
Avicel	80 mg
PVPPXL	20 mg
Aerosil	2 mg
Magnesium stearate	5 mg
Total	447 mg

Manufacture: The active ingredient is mixed with the carrier materials and compressed by means of a tabletting machine (Korsch EKO, Stempeldurchmesser 10 mm).

Example 40

Capsules

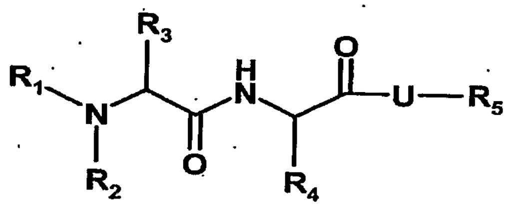
Capsules, comprising, as active ingredient, 100 mg of any one of the compounds of formula (I) given in Examples **8-37**, of the following composition are prepared according to standard procedures:

Composition:	
Active Ingredient	100 mg
Avicel	200 mg
PVPPXL	15 mg
Aerosil	2 mg
Magnesium stearate	1.5 mg
Total	318.5 mg

Manufacturing is done by mixing the components and filling them into hard gelatine capsules, size 1.

We claim:

1. A compound according to formula I



I

wherein

R_1 is H; C_1-C_4 alkyl, C_1-C_4 alkenyl, C_1-C_4 alkynyl or cycloalkyl which are unsubstituted or substituted;

R_2 is H, C_1-C_4 alkyl, C_1-C_4 alkenyl, C_1-C_4 alkynyl or cycloalkyl which are unsubstituted or substituted;

R_3 is H, $-CF_3$, $-C_2F_5$, C_1-C_4 alkyl, C_1-C_4 alkenyl, C_1-C_4 alkynyl; $-CH_2$-Z or R_2 and R_3 together with the nitrogen form a het ring;

Z is H, –OH, F, Cl, $-CH_3$; $-CF_3$, $-CH_2Cl$, $-CH_2F$ or $-CH_2OH$;

R_4 is C_1-C_{16} straight or branched alkyl, C_1-C_{16} alkenyl, C_1-C_{16} alkynyl, or cycloalkyl, -$(CH_2)_{1-6}$-Z_1, -$(CH_2)_{0-6}$-phenyl, and -$(CH_2)_{0-6}$-het, wherein alkyl, cycloalkyl and phenyl are unsubstituted or substituted;

Z_1 is –N(R_8)-C(O)-C_1-C_{10}alkyl, –N(R_8)-C(O)-$(CH_2)_{1-6}$-C_3-C_7-cycloalkyl, –N(R_8)-C(O)-$(CH_2)_{0-6}$-phenyl, –N(R_8)-C(O)-$(CH_2)_{1-6}$-het, -C(O)-N(R_9)(R_{10}), -C(O)-O-C_1-C_{10}alkyl, -C(O)-O-$(CH_2)_{1-6}$-C_3-C_7-cycloalkyl, -C(O)-O-$(CH_2)_{0-6}$-phenyl, -C(O)-O-$(CH_2)_{1-6}$-het, -O-C(O)-C_1-C_{10}alkyl, -O-C(O)-$(CH_2)_{1-6}$-C_3-C_7-cycloalkyl, -O-C(O)-$(CH_2)_{0-6}$-phenyl, -O-C(O)-$(CH_2)_{1-6}$-het, wherein alkyl, cycloalkyl and phenyl are unsubstituted or substituted;

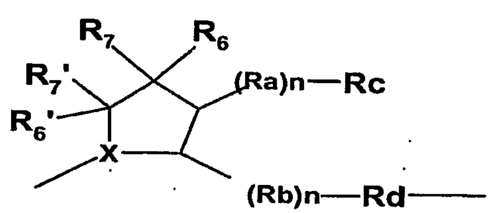
het is a 5-7 membered heterocyclic ring containing 1- 4 heteroatoms selected from N, O and S, or an 8-12 membered fused ring system including at least one 5-7

membered heterocyclic ring containing 1, 2 or 3 heteroatoms selected from N, O, and S, which heterocyclic ring or fused ring system is unsubstituted or substituted on a carbon or nitrogen atom;

R_8 is H, $-CH_3$, $-CF_3$, $-CH_2OH$ or CH_2Cl;
R_9 and R_{10} are each independently H, C_1-C_4alkyl, C_3-C_7-cycloalkyl, $-(CH_2)_{1-6}$-C_3-C_7-cycloalkyl, $-(CH_2)_{0-6}$-phenyl, wherein alkyl, cycloalkyl and phenyl are unsubstituted or substituted, or R_9 and R_{10} together with the nitrogen form het;

R_5 is H, C_1-C_{10}-alkyl, C_3-C_7-cycloalkyl, $-(CH_2)_{1-6}$-C_3-C_7-cycloalkyl, $-C_1$-C_{10}-alkyl-aryl, $-(CH_2)_{0-6}$-C_3-C_7-cycloalkyl-$(CH_2)_{0-6}$-phenyl, $-(CH_2)_{0-4}CH$-$((CH_2)_{1-4}$-phenyl$)_2$, $-(CH_2)_{0-6}$-$CH(phenyl)_2$, -indanyl, $-C(O)$-C_1-C_{10}alkyl, $-C(O)$-$(CH_2)_{1-6}$-C_3-C_7-cycloalkyl, $-C(O)$-$(CH_2)_{0-6}$-phenyl, $-(CH_2)_{0-6}$-het, $-C(O)$-$(CH_2)_{1-6}$-het, or R_5 is a residue of an amino acid, wherein the alkyl, cycloalkyl, phenyl and aryl substituents are unsubstituted or substituted;

U is a as shown in structure II:



II

wherein
n = 0-5;
X is –CH or N;
Ra and Rb are independently an O, S, or N atom or C_{0-8} alkyl wherein one or more of the carbon atoms in the alkyl chain may be replaced by a heteroatom selected from O, S or N, and where the alkyl may be unsubstituted or substituted;
Rd is selected from:

(a) -Re – Q – (Rf)(Rg); or

(b) Ar_1–D– Ar_2 ;

Rc is H or Rc and Rd may together form a cycloalkyl or het; where if Rd and Rc form a cycloalkyl or het, R_5 is attached to the formed ring at a C or N atom;

Re is C_{1-8} alkyl which may be unsubstituted or substituted;
Q is N, O, S, S(O), or $S(O)_2$;
Ar_1 and Ar_2 are substituted or unsubstituted aryl or het;

Rf and Rg are each independently H or substituted or unsubstituted C_0-C_{10}-alkyl or C_1-C_{10}- alkylphenyl;

D is –CO–, or C_{1-7} alkyl, aryl which may be unsubstituted or substituted with one or more halogens, OH, -O-C_1-C_6alkyl, -S-C_1-C_6alkyl or –CF_3;

R_6, R_7, R'_6 and R'_7 are each independently H, -C_1-C_{10} alkyl, -OH, -O-C_1-C_{10}-alkyl, -$(CH_2)_{0-6}$-C_3-C_7-cycloalkyl, -O-$(CH_2)_{0-6}$-aryl, phenyl, -$(CH_2)_{1-6}$-het, -O-$(CH_2)_{1-6}$-het, -OR_{11}, -C(O)-R_{11}, –C(O)-N(R_{11})(R_{12}), -N(R_{11})(R_{12}), -S-R_{11}, -S(O)-R_{11}, -$S(O)_2$-R_{11}, -$S(O)_2$-$NR_{11}R_{12}$, -NR_{11}-$S(O)_2$- R_{12}, wherein alkyl, cycloalkyl and aryl are unsubstituted or substituted; and R_6, R_7, R'_6 and R'_7 can be united to form a ring system;

R_{11} and R_{12} are independently H, C_1-C_{10} alkyl, -$(CH_2)_{0-6}$-C_3-C_7-cycloalkyl, -$(CH_2)_{0-6}$-$(CH)_{0-1}$$(aryl)_{1-2}$, -C(O)-$C_1$-$C_{10}$alkyl, -C(O)-$(CH_2)_{1-6}$-$C_3$-$C_7$-cycloalkyl, -C(O)-O-$(CH_2)_{0-6}$-aryl, -C(O)-$(CH_2)_{0-6}$-O-fluorenyl, -C(O)-NH-$(CH_2)_{0-6}$-aryl, -C(O)-$(CH_2)_{0-6}$-aryl, -C(O)-$(CH_2)_{1-6}$-het, -C(S)-$C_1$-$C_{10}$alkyl, -C(S)-$(CH_2)_{1-6}$-$C_3$-$C_7$-cycloalkyl, -C(S)-O-$(CH_2)_{0-6}$-aryl, -C(S)-$(CH_2)_{0-6}$-O-fluorenyl, -C(S)-NH-$(CH_2)_{0-6}$-aryl, -C(S)-$(CH_2)_{0-6}$-aryl, -C(S)-$(CH_2)_{1-6}$-het, wherein alkyl, cycloalkyl and aryl are unsubstituted or substituted; or R_{11} and R_{12} are a substituent that facilitates transport of the molecule across a cell membrane; or R_{11} and R_{12} together with the nitrogen atom form het;

wherein the alkyl substituents of R_{11} and R_{12} may be unsubstituted or substituted by one or more substituents selected from C_1-C_{10}, halogen, OH, -O-C_1-C_6alkyl, -S-C_1-C_6alkyl or –CF_3;

substituted cycloalkyl substituents of R_{11} and R_{12} are substituted by one or more substituents selected from a C_1-C_{10} alkene, C_1-C_6alkyl, halogen, OH, -O-C_1-C_6alkyl, -S-C_1-C_6alkyl or –CF_3; and

substituted phenyl or aryl of R_{11} and R_{12} are substituted by one or more substituents selected from halogen, hydroxy, C_1-C_4 alkyl, C_1-C_4 alkoxy, nitro, -CN, -O-C(O)-C_1-C_4alkyl and –C(O)-O-C_1-C_4-aryl,

or pharmaceutically acceptable salts thereof.

2. A compound formula (I) according to claim 1 wherein

R_1 is H; C_1-C_4 alkyl, C_1-C_4 alkenyl, C_1-C_4 alkynyl or cycloalkyl which are unsubstituted or substituted by one or more substituents selected from halogen, -OH, -SH, -OCH_3, -SCH_3, -CN, -SCN and nitro;

R_2 is H, C_1-C_4alkyl, C_1-C_4 alkenyl, C_1-C_4 alkynyl or cycloalkyl which are unsubstituted or substituted by one or more substituents selected from halogen, -OH, -SH, -OCH_3, -SCH_3, -CN, -SCN and nitro;

R_3 is H, -CF_3, -C_2F_5, C_1-C_4 alkyl, C_1-C_4 alkenyl, C_1-C_4 alkynyl; –CH_2-Z or R_2 and R_3 together with the nitrogen form a het;

Z is H, –OH, F, Cl, –CH_3; -CF_3, -CH_2Cl, -CH_2F or –CH_2OH;

R_4 is C_1-C_{16} straight or branched alkyl, C_1-C_{16} alkenyl, C_1-C_{16} alkynyl, or cycloalkyl, -$(CH_2)_{1-6}$-Z_1, -$(CH_2)_{0-6}$-phenyl, and –$(CH_2)_{0-6}$-het, wherein alkyl, cycloalkyl and phenyl are unsubstituted or substituted;

Z_1 is –N(R_8)-C(O)-C_1-C_{10}alkyl, –N(R_8)-C(O)-$(CH_2)_{1-6}$-C_3-C_7-cycloalkyl, –N(R_8)-C(O)-$(CH_2)_{0-6}$-phenyl, –N(R_8)-C(O)-$(CH_2)_{1-6}$-het, -C(O)-N(R_9)(R_{10}), -C(O)-O-C_1-C_{10}alkyl, -C(O)-O-$(CH_2)_{1-6}$-C_3-C_7-cycloalkyl, -C(O)-O-$(CH_2)_{0-6}$-phenyl, -C(O)-O-$(CH_2)_{1-6}$-het, -O-C(O)-C_1-C_{10}alkyl, -O-C(O)-$(CH_2)_{1-6}$-C_3-C_7-cycloalkyl, -O-C(O)-$(CH_2)_{0-6}$-phenyl, -O-

$C(O)-(CH_2)_{1-6}$-het, wherein alkyl, cycloalkyl and phenyl are unsubstituted or substituted;

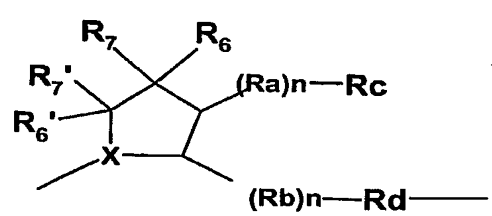
het is a 5-7 membered heterocyclic ring containing 1- 4 heteroatoms selected from N, O and S, or an 8-12 membered fused ring system including at least one 5-7 membered heterocyclic ring containing 1, 2 or 3 heteroatoms selected from N, O, and S, which heterocyclic ring or fused ring system is unsubstituted or substituted on a carbon atom by halogen, hydroxy, C_1-C_4alkyl, C_1-C_4 alkoxy, nitro, -O-C(O)-C_1-C_4alkyl or –C(O)-O-C_1-C_4-alkyl or on a nitrogen by C_1-C_4 alkyl, -O-C(O)-C_1-C_4alkyl or –C(O)-O-C_1-C_4-alkyl;

R_8 is H, $-CH_3$, $-CF_3$, $-CH_2OH$ or CH_2Cl;

R_9 and R_{10} are each independently H, C_1-C_4alkyl, C_3-C_7-cycloalkyl, $-(CH_2)_{1-6}$-C_3-C_7-cycloalkyl, $-(CH_2)_{0-6}$-phenyl, wherein alkyl, cycloalkyl and phenyl are unsubstituted or substituted, or R_9 and R_{10} together with the nitrogen form het;

R_5 is H, C_1-C_{10}-alkyl, C_3-C_7-cycloalkyl, $-(CH_2)_{1-6}$-C_3-C_7-cycloalkyl, -C_1-C_{10}-alkyl-aryl, -$(CH_2)_{0-6}$-C_3-C_7-cycloalkyl-$(CH_2)_{0-6}$-phenyl, $-(CH_2)_{0-4}CH$-$((CH_2)_{1-4}$-phenyl$)_2$, $-(CH_2)_{0-6}$-CH(phenyl$)_2$, -indanyl, -C(O)-C_1-C_{10}alkyl, -C(O)-$(CH_2)_{1-6}$-C_3-C_7-cycloalkyl, -C(O)-$(CH_2)_{0-6}$-phenyl, $-(CH_2)_{0-6}$-het , -C(O)-$(CH_2)_{1-6}$-het, or R_5 is a residue of an amino acid, wherein alkyl, cycloalkyl, phenyl and aryl are unsubstituted or substituted;

U is a as shown in structure II:



II

wherein

n = 0-5;

X is –CH or N;

Ra and Rb are independently an O, S, or N atom or C_{0-8} alkyl wherein one or more of the carbon atoms in the alkyl chain may be replaced by a heteroatom selected from O, S or N, and where the alkyl may be unsubstituted or substituted;

Rd is selected from:

(a) Re – Q – (Rf)(Rg) ; or

(b) Ar_1–D– Ar_2 ;

Rc is H or Rd and Rc together form cycloalkyl or het; where if Rd and Rc form a cycloalkyl or heteroring, R_5 is attached to the formed ring at a C or N atom;

Re is C_{1-8} alkyl which may be unsubstituted or substituted;

Q is N, O, S, S(O), or $S(O)_2$;

Ar_1 and Ar_2 are substituted or unsubstituted aryl or het;

Rf and Rg are each independently H or substituted or unsubstituted C_0-C_{10}-alkyl, or C_1-C_{10}-alkylaryl;

D is –CO-, or C_{1-7} alkyl which may be unsubstituted or substituted with one or more halogens, OH, -O-, C_1-C_6alkyl, -S-C_1-C_6alkyl or –CF_3;

and R_6, R_7, R'_6 and R'_7 are each independently H, -C_1-C_{10} alkyl, -OH, -O-C_1-C_{10}-alkyl, -$(CH_2)_{0-6}$-C_3-C_7-cycloalkyl, -O-$(CH_2)_{0-6}$-aryl, phenyl, -$(CH_2)_{1-6}$-het, -O-$(CH_2)_{1-6}$-het, -OR_{11}, -C(O)-R_{11}, –C(O)-N(R_{11})(R_{12}), -N(R_{11})(R_{12}), -S-R_{11}, -S(O)-R_{11}, -$S(O)_2$-R_{11}, -$S(O)_2$-$NR_{11}R_{12}$, -NR_{11}-$S(O)_2$- R_{12}, wherein alkyl, cycloalkyl and aryl are unsubstituted or substituted; or any R_6, R_7, R'_6 and R'_7 can be united to form a ring system;

R_{11} and R_{12} are independently H, C_1-C_{10} alkyl, -$(CH_2)_{0-6}$-C_3-C_7-cycloalkyl, -$(CH_2)_{0-6}$-$(CH)_{0-1}$$(aryl)_{1-2}$, -C(O)-$C_1$-$C_{10}$alkyl, -C(O)-$(CH_2)_{1-6}$-$C_3$-$C_7$-cycloalkyl, -C(O)-O-$(CH_2)_{0-6}$-aryl, -C(O)-$(CH_2)_{0-6}$-O-fluorenyl, -C(O)-NH-$(CH_2)_{0-6}$-aryl, -C(O)-$(CH_2)_{0-6}$-aryl, -C(O)-$(CH_2)_{1-6}$-het, -C(S)-$C_1$-$C_{10}$alkyl, -C(S)-$(CH_2)_{1-6}$-$C_3$-$C_7$-cycloalkyl, -C(S)-O-$(CH_2)_{0-6}$-aryl, -C(S)-$(CH_2)_{0-6}$-O-fluorenyl, -C(S)-NH-$(CH_2)_{0-6}$-aryl, -C(S)-$(CH_2)_{0-6}$-aryl, -C(S)-

$(CH_2)_{1\text{-}6}$-het, wherein alkyl, cycloalkyl and aryl are unsubstituted or substituted; or R_{11} and R_{12} are a substituent that facilitates transport of the molecule across a cell membrane; or R_{11} and R_{12} together with the nitrogen are het; aryl of R_{11} and R_{12} can be phenyl, naphthyl, or indanyl which is unsubstituted or substituted;

alkyl of R_{11} and R_{12} may be unsubstituted or substituted by one or more substituents selected from a C_1-C_{10} alkene, halogen, OH, -O-C_1-C_6alkyl, -S-C_1-C_6alkyl and –CF_3;

cycloalkyl of R_{11} and R_{12} may be unsubstituted or substituted by one or more selected from a C_1-C_{10} alkene, one or more halogens, C_1-C_6alkyl, halogen, OH, -O-C_1-C_6alkyl, -S-C_1-C_6alkyl or –CF_3; and

phenyl or aryl of R_{11} and R_{12} may be unsubstituted or substituted by one or more substituents selected from halogen, hydroxy, C_1-C_4 alkyl, C_1-C_4 alkoxy, nitro, -CN, -O-C(O)-C_1-C_4alkyl and –C(O)-O-C_1-C_4-aryl;

or pharmaceutically acceptable salts thereof.

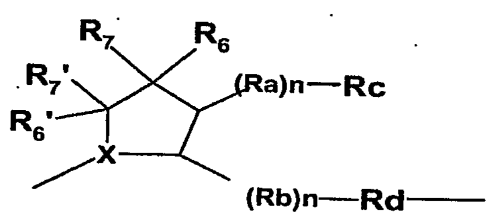
3. A compound of formula I according to claim 1 wherein

R_1 and R_2 are independently H or substituted or unsubstituted C_1-C_4alkyl;

R_4 is C_1-C_{16} straight or branched alkyl, or cycloalkyl, wherein the alkyl or cycloalkyl may be unsubstituted or substituted;

R_5 is H, C_1-C_{10}-alkyl, C_1-C_{10}-alkyl-aryl, indanyl, naphthyl or R_5 is a residue of an amino acid, wherein the alkyl or aryl substituents are unsubstituted or substituted;

U is a as shown in structure II:



II

wherein

n = 0-5;

X is –CH or N;

Ra and Rb are independently an O, S, or N atom or C_{0-8} alkyl wherein one or more of the carbon atoms in the alkyl chain may be replaced by a heteroatom selected from O, S or N, and where the alkyl may be unsubstituted or substituted;

Rd is selected from

(a) --Re – Q – (Rf)(Rg); or

(b) Ar_1–D– Ar_2;

Rc is H or Rc and Rd together form cycloalkyl or het; where if Rd and Rc form a cycloalkyl or heteroring, R_5 is attached to the formed ring at a C or N atom;

Re is C_{1-8} alkyl which may be unsubstituted or substituted;

Q is N, O, S, S(O), or $S(O)_2$;

Ar_1 and Ar_2 are substituted or unsubstituted aryl or het;

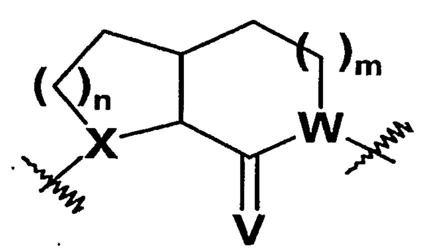
Rf and Rg are each independently H or substituted or unsubstituted C_0-C_{10}-alkyl or C_a-C_{10}-alkyl aryl;

D is –CO-, or C_{1-7} alkyl which may be unsubstituted or substituted with one or more halogens, OH, -O-C_1-C_6alkyl, -S-C_1-C_6alkyl or -CF_3;

and R_6, R_7, R'_6 and R'_7 are each independently H, -C_1-C_{10} alkyl, or –OH, alkoxy, or aryloxy;

or pharmaceutically acceptable salts thereof.

4. A compound according to claim 3 wherein U is a bicyclic saturated or unsaturated ring system, consisting of all carbon skeleton or with one or more heteroatoms such as O, N, S but preferably as shown in structure III:



III

wherein

wherein any of the ring carbon atoms can be unsubstituted or substituted with any of the substituted defined above as R_6, R_7, $R_{6'}$ and $R_{7'}$;

X is CH or N;

V is O, F_2, Cl_2, Br_2, I_2, S, YH, H_2, NH, C_1-C_4 alkyl;

W is -CH, -N;

n is 0-3; and

m is 0-3.

5. A compound according to claim 4 wherein the ring carbons on U are unsubstituted or independently substituted by a substituent selected from halo, H, OH, lower alkyl or lower alkoxy, wherein alkyl or alkoxy are unsubstituted or substituted by halogen, OH, lower alkyl or lower alkoxy.

6. A compound of formula (I) according to claim 4 wherein

R_1 and R_3 are methyl or ethyl;

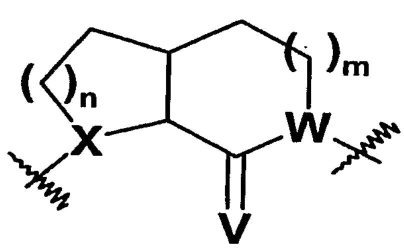
R_2 is H, methyl, ethyl, chloromethyl, dichloromethyl or trifluoromethyl;

R_4 is C_1-C_4alkyl or C_3-C_7 cycloalkyl particularly isopropyl, t-butyl, cyclopentyl, or cyclohexyl;

R_5 is -C_1-C_4-alkyl-phenyl, particularly phenylmethyl, phenylethyl and phenylpropyl; indanyl, naphthyl;

R_6 and R_7 are H or methyl;

U has the structure of formula III:



III

wherein

wherein any of the ring carbon atoms can be unsubstituted or substituted with any of the substituted defined above for R_6, R_7, $R_{6'}$ and R_7';

X is N;

V is O or H_2;

W is -N;

n is 1; and

m is 1 or 2.

7. A compound of formula (I) according to claim 4 wherein

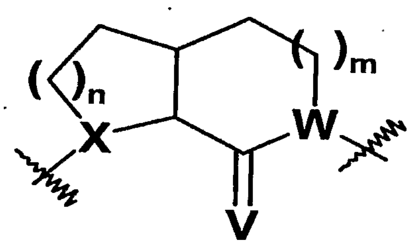
R_1 and R_3 are methyl or ethyl;

R_2 is H;

R_4 is isopropyl, t-butyl, cyclopentyl, or cyclohexyl;

R_5 is -C_1-C_4-alkyl-phenyl, particularly phenylethyl and indanyl;

U has the structure of formula III:



III

wherein

wherein any of the ring carbon atoms can be unsubstituted or substituted with any of the substituted defined above for R_6, R_7, $R_{6'}$ and R_7';

X is N;

V is O or H_2;

W is -N;

n is 1; and

m is 1 or 2.

8. A compound of formula (I) according to claim 1 wherein

R_1 and R_3 are methyl or ethyl;

R_2 is especially H, methyl, ethyl, chloromethyl, dichloromethyl or trifluoromethyl;

R_4 is C_1-C_4alkyl or C_3-C_7 cycloalkyl particularly isopropyl, t-butyl, cyclopentyl, or cyclohexyl;

R_5 is H;

U has the structure of formula II wherein

X is N;

R_6, R'_6, R_7, and R'_7 are H;

n is O;

Rc is H;

Ar_1 and Ar_2 are phenyl and D is C_1 alkyl.

9. A compound of formula (I) according to claim 1 wherein

R_1 and R_3 are methyl or ethyl;

R_2 is H, methyl, ethyl, chloromethyl, dichloromethyl or trifluoromethyl;

R_4 is C_1-C_4alkyl or C_3-C_7 cycloalkyl particularly isopropyl, t-butyl, cyclopentyl, or cyclohexyl;

R_5 is H, indanyl or phenyl;

U has the structure of formula II wherein

X is N;

Q is O;

R_6, R'_6, R_7, and R'_7 are H;

n is O;

Rc is H;

Re is C_1 alkyl; and

R_g and R_f are C_o alkyl.

10. A compound of formula (I) according to claim 1 wherein

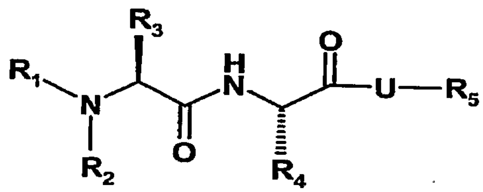
R_1 and R_3 are methyl or ethyl;

R_2 is H, methyl, ethyl, chloromethyl, dichloromethyl or trifluoromethyl;

R_4 is C_1-C_4alkyl or C_3-C_7 cycloalkyl particularly isopropyl, t-butyl, cyclopentyl, or cyclohexyl;
R_5 is H, indanyl or phenyl;
U has the structure of formula II wherein
X is N;
Q is N;
R_6, R'_6, R_7, and R'_7 are H;
n is O;
Rc is H;
Re is C_1 alkyl; and
R_g is C_1 alkyl, C_2 alkyl, C_2 alkylphenyl;
and R_f is C_2 alkyl or C_2 alkylphenyl.

11. A compound of formula (I) according to claim 1 wherein
R_1 and R_3 are preferably methyl or ethyl;
R_2 is especially H, methyl, ethyl, chloromethyl, dichloromethyl or trifluoromethyl;
R_4 is C_1-C_4alkyl or C_3-C_7 cycloalkyl particularly isopropyl, t-butyl, cyclopentyl, or cyclohexyl;
R_5 is phenyl;
U has the structure of formula II wherein
X is N;
Q is S, S(O) or $S(O)_2$;
R_6, R'_6, R_7, and R'_7 are H;
n is O;
Re is C_1 alkyl;
R_g is C_0 alkyl
and R_f is C_2 alkyl.

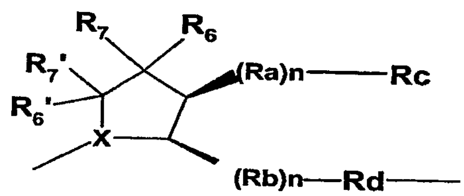
12. A compound of formula I have the stereochemistry of formula IV:



IV

R_1, R_2 R_3, R_4, R_5 and U are as defined in claim 1.

13. A compound of formula I wherein U has the stereochemistry of formula V:



V

14. A pharmaceutical composition which comprises a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of formula I according to claim 1.

15. A method of treating a proliferative disease which comprises administering a therapeutically effective amount of a compound of formula I according to claim 1 to a mammal in need of such treatment.

16. A method of claim 15 wherein the mammal is a human.

17. A compound selected from:

N-[1-Cyclohexyl-2-oxo-2-(6-phenethyl-octahydro-pyrrolo[2,3-*c*]pyridin-1-yl)-ethyl]-2-methylamino-acetamide;

2-Methylamino-*N*-[2-methyl-1-(7-oxo-6-phenethyl-octahydro-pyrrolo[2,3-*c*]pyridine-1-carbonyl)-propyl]-propionamide;

2-Methylamino-*N*-[2-methyl-1-(7-oxo-6-phenethyl-octahydro-pyrrolo[2,3-*c*]pyridine-1-carbonyl)-propyl]-propionamide;

2-Methylamino-*N*-[2-methyl-1-(8-oxo-7-phenethyl-octahydro-pyrrolo[2,3-*c*]azepine-1-carbonyl)-propyl]-propionamide;

2-Methylamino-*N*-[2-methyl-1-(7-oxo-6-phenethyl-octahydro-pyrrolo[2,3-*c*]pyridine-1-carbonyl)-propyl]-butyramide;

2-Methylamino-*N*-[2-methyl-1-(7-oxo-6-phenethyl-octahydro-pyrrolo[2,3-*c*]pyridine-1-carbonyl)-propyl]-butyramide;

2-Methylamino-*N*-[2-methyl-1-(8-oxo-7-phenethyl-octahydro-pyrrolo[2,3-*c*]azepine-1-carbonyl)-propyl]-butyramide;

N-[1-Cyclohexyl-2-oxo-2-(7-oxo-6-phenethyl-octahydro-pyrrolo[2,3-*c*]pyridin-1-yl)-ethyl]-2-methylamino-propionamide;

2-Methylamino-*N*-{2-methyl-1-[5-(3-methyl-hexa-3,5-dienyl)-6-oxo-hexahydro-pyrrolo[3,4-*b*]pyrrole-1-carbonyl]-propyl}-propionamide;

2-Methylamino-*N*-[2-methyl-1-(3-methyl-7-oxo-6-phenethyl-octahydro-pyrrolo[2,3-*c*]pyridine-1-carbonyl)-propyl]-propionamide;

2-Methylamino-*N*-[2-methyl-1-(3-methyl-7-oxo-6-phenethyl-octahydro-pyrrolo[2,3-*c*]pyridine-1-carbonyl)-propyl]-propionamide;

N-[1-(4-Benzyloxy-7-oxo-6-phenethyl-octahydro-pyrrolo[2,3-*c*]pyridine-1-carbonyl)-2-methyl-propyl]-2-methylamino-propionamide;

N-[1-Cyclohexyl-2-oxo-2-(8-oxo-7-phenethyl-octahydro-pyrrolo[2,3-*c*]azepin-1-yl)-ethyl]-2-methylamino-butyramide;

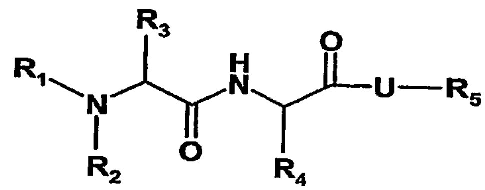
N-[1-Cyclohexyl-2-oxo-2-(8-oxo-7-phenethyl-octahydro-pyrrolo[2,3-*c*]azepin-1-yl)-ethyl]-2-methylamino-butyramide;

N-[1-Cyclohexyl-2-oxo-2-(7-phenethyl-octahydro-pyrrolo[2,3-*c*]azepin-1-yl)-ethyl]-2-methylamino-propionamide; and

2-Methylamino-*N*-[2-methyl-1-(8-oxo-7-phenethyl-octahydro-pyrrolo[2,3-*c*]azepine-1-carbonyl)-propyl]-butyramide.

Abstract of the Disclosure

Novel compounds that inhibit the binding of the Smac protein to Inhibitor of Apoptosis Proteins (IAPs) of the formula I



(I)